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REVIEW

Chemotherapy for hepatocellular carcinoma: The present and the future

Marco Le Grazie, Maria Rosa Biagini, Mirko Tarocchi, Simone Polvani, Andrea Galli

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver. Its relationship to chronic liver diseases, in particular cirrhosis, develops on a background of viral hepatitis, excessive alcohol intake or metabolic steatohepatitis, leads to a high incidence and prevalence of this neoplasia worldwide. Despite the spread of HCC, its treatment it's still a hard challenge, due to high rate of late diagnosis and to lack of therapeutic options for advanced disease. In fact radical surgery and liver transplantation, the most radical therapeutic approaches, are indicated only in case of early diagnosis. Even local therapies, such as transarterial chemoembolization, find limited indications, leading to an important problem regarding treatment of advanced disease. In this situation, until terminal HCC occurs, systemic therapy is the only possible approach, with sorafenib as the only standard treatment available. Anyway, the efficacy of this drug is limited and many efforts are necessary to understand who could benefit more with this treatment. Therefore, other molecules for a targeted therapy were evaluated, but only regorafenib showed promising results. Beside molecular target therapy, also cytotoxic drugs, in particular oxaliplatin- and gemcitabine-based regimens, and immune-check-point inhibitors were tested with interesting results. The future of the treatment of this neoplasia is linked to our ability to understand its mechanisms of resistance and to find novel therapeutic targets, with the objective to purpose individualized approaches to patients affected by advanced HCC.

Key words: Hepatocellular carcinoma; Systemic therapy; Chemotherapy; Molecular targeted therapy; Cytotoxic therapy; Immunotherapy; Perspectives

Core tip: The aim of this review is to make a point on chemotherapeutic options for treatment of hepatocellular carcinoma (HCC) at advanced stage, the most frequent stage of presentation of this neoplasia, still characterized

by an important mortality rate. By now, sorafenib is the only standard treatment, but other options were recently studied and will be soon available for clinicians and patients affected by HCC. The review can be divided in four sections: The first one regards molecular target therapy and are described sorafenib, its open issues, but also other drugs with similar targets that have been evaluated for treatment of HCC. The second and the third parts regard cytotoxic drugs and immunotherapy, respectively, which were evaluated in recent years as possible alternatives or adjuvant to Sorafenib. In the last part of the review, future perspectives are described, in particular for what concerns resistance mechanism of the neoplasia, delivery methods or biological enhancers for drugs already in use, new drugs that will be probably evaluated and molecular targets that could soon become eligible for target therapy hopefully leading to the development of personalized therapy.

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INTRODUCTION

According to last EASL-EORTC guidelines, liver cancer is the sixth most common cancer, the third cause of cancer related death, and accounts for 7% of all cancers. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is a major global health problem. Its incidence reaches a peak at median age of 70 years, which results to be higher in Japanese population (70-79 years) and lower in Chinese and Black African populations. HCC appears to be more frequent in males than in females (2.4:1)[1].

HCC development is often related to the presence of a chronic liver, which represents one of the most important risk factors for this neoplasia. In particular cirrhosis, which can occur as a consequence of chronic viral hepatitis, excessive alcohol intake, nonalcoholic fatty liver disease or genetic diseases (*e.g.*, hemochromatosis), is a frequent setting for HCC onset as well as a cause of liver dysfunction.

Liver dysfunction, in addition to high heterogeneity regarding the mechanisms of carcinogenesis and to the frequent diagnosis of HCC at an advanced stage despite appropriate screening in particular regarding viral chronic hepatitis, lead to great difficulty in treating this neoplasia, as well as in developing new therapeutic alternatives.

Surgery and liver transplantation (OLT) in fact represent the only radical treatments of this disease, but, as mentioned, are not feasible in case of advanced disease or significant hepatic dysfunction[2]. In particular, according to EASL indications based on Barcelona-Clínic Liver Cancer (BCLC) classification related on prognostic variables, surgery is proposable in very early stage HCC (stage 0), while OLT is indicated for early stage disease (stage A). More advanced diseases are treated with, in order: Radiofrequency ablation (RFA), transarterial chemoembolization (TACE) or sorafenib, while terminal HCC (stage D) has best supportive care as unique therapeutic option[1]. RFA and TACE are treatment of choice in case of early stage disease (stage A) with associated diseases and in case of intermediate stage disease (stage B) respectively, while other non-surgical approaches as transarterial radiation, percutaneous ethanol injection and microwave ablation are still infrequently used in clinical practice because of partial or less encouraging results compared with TACE and RFA[3,4].

Of particular interest is the approach with TACE, which, in addition to its purely therapeutic indication, has shown utility for its ability to lead to the down-staging of the disease[4,5] and for its neo-adjuvant effect[6]. For this reason, the TACE has been subject to intense technical development, which has led to, in addition to the conventional method Lipiodol-TACE, new approaches such as drug-eluting beads TACE (DEB-TACE)[7], based on doxorubicin and on administration as microspheres, with encouraging results.

In case of TACE resistance or advanced stage HCC (stage C), compatibly with the residual liver function, systemic chemotherapy is indicated, but sorafenib is currently the only standard systemic treatment available[8,9]. In consideration of the frequent approach to advanced HCC, and given the lack of viable alternatives, many efforts in the field of research have been made to optimize the use of sorafenib, for example by using it together with TACE or with hepatic arterial infusion chemotherapy (HAIC), and to evaluate chemotherapy regimens and other small molecules already in use for other types of malignancies or under development. The aim of our review is to evaluate the available options and future possible strategies regarding systemic therapy for HCC.

MOLECULAR TARGETED THERAPY

As previously said, sorafenib is the only standard treatment available for advanced HCC. In the wake of the good results obtained with sorafenib, numerous other small molecules were evaluated for the treatment of this neoplasia.

Sorafenib

The action of sorafenib is expressed on various molecular targets involved in the mechanism of tumor growth and angiogenesis, leading to their inhibition: Serine-threonine kinases Raf-1 and B-Raf involved in RAF/MEK/ERK pathway, RET, FLT-3, the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2 and 3 and platelet-

derived growth factor receptor β (PDGFR-β)[10-13]. The efficacy of this drug in treating Child-Pugh A stage C HCC was demonstrated in two phase Ⅲ, randomized, placebo-controlled clinical trials: the SHARP trial[8] and the Asia-Pacific study (ORIENTAL)[9]. The SHARP trial compared Sorafenib treatment (400 mg twice a day) to placebo among 602 patients, showing a significant difference in overall survival (10.7 mo *vs* 7.9 mo, $P < 0.001$), time to radiologic progression (5.5 mo *vs* 2.8 mo, $P < 0.001$) and disease control rate (43% *vs* 32%, $P = 0.002$), even if no significant difference was observed in time to symptomatic progression (4.1 mo *vs* 4.9 mo, $P = 0.77$). The observed side effects were diarrhea, weight loss, hand-foot syndrome and hypophosphatemia.

The ORIENTAL trial had a design similar to the SHARP study but was performed on 226 patients from the Asia-Pacific region: The overall survival was significantly increased in the Sorafenib-treated group (6.5 mo *vs* 4.2 mo, $P = 0.014$), even if the overall survival was lower compared to the SHARP study; more encouraging results were observed evaluating the time to progression, which was significantly higher in the Sorafenib group (2.8 mo *vs* 1.4 mo, $P = 0.0005$).

The eligibility criteria for treatment with sorafenib are still relatively restrictive and few data are available regarding its use in the presence of impaired liver function (Child-Pugh B/C) or in elderly patients. Regarding liver function, available data come from retrospective studies[14-18], that evaluated treatment with sorafenib in patients with liver function Child-Pugh B, showing shorter overall survival in these patients, compared with patients with Child-Pugh A. In addition, two studies[15-18] showed an increased incidence of severe adverse events in Child-Pugh B patients, that led to dose reduction or discontinuation of treatment. Thus, in the latest available guidelines there is no clear contraindication about sorafenib administration in patients with Child-Pugh B, but caution is advised due to the increased risk of side effects[19]. Sorafenib treatment in elderly (age > 70 years) was evaluated only in a retrospective study[20], which reported a progression free survival and overall survival similar to younger patients, associated to a higher incidence of some adverse events (neutropenia, malaise and mucositis); anyway, no clear indication about treatment of older patients was given in last guidelines. Beside the evaluation of therapeutic usefulness of sorafenib in single therapy, numerous studies have evaluated its use as adjuvant or neoadjuvant treatment. As previously said, potential down-staging effect was suggested, leading to a possible use of this drug as neo-adjuvant therapy or as bridge-to-transplantation therapy[21]; in particular some studies suggest a possible role of sorafenib in preventing tumor relapse after liver transplantation[22,23], even if available studies were performed on small samples not providing statistically significant results. Unfortunately, the same optimism placed in the use of this drug for a neoadjuvant therapy does not seem to be confirmed regarding its use with adjuvant intent. In 2015, the STORM trial, a randomized, double blind, placebo controlled trial, evaluated sorafenib efficacy as adjuvant after resection or local ablation, but no difference in median recurrence free survival was observed (33.3 mo *vs* 33.7 mo, $P = 0.26$)[24]. A more in-depth discussion should be done about the combination of sorafenib and TACE: Initial encouraging results came from retrospective studies[25,26] that evaluated sorafenib in case of TACE refractory or ineligibility (reduced efficacy of TACE itself, vascular devastation, involvement of complex extrahepatic blood supply routes, vascular invasion, distant metastases)[27]. Despite this, initial randomized trial to evaluate this combination did not confirm the efficacy of TACE + sorafenib. In particular, the SPACE trial[28] showed no difference between TACE + sorafenib *vs* TACE + placebo regarding time-to-tumor progression (169 d *vs* 166 d, $P = 0.072$) and overall survival (554 d *vs* 562 d, $P = 0.295$); a more recent phase Ⅲ randomized trial from Kudo *et al*[29] with a similar design confirmed those results (time to tumor progression 5.4 mo *vs* 3.7 mo, $P = 0.252$; overall survival 29.7 mo *vs* NE, $P = 0.072$). Recent observational studies[30,31] showed more encouraging results in terms of progression free survival and overall survival respectively, and a systematic review/meta-analysis[32] reported a significant different among TACE + sorafenib *vs* TACE in terms of response rate (OR = 3.59, 95%CI: 1.74-7.39, $I^2 = 21\%$, $P = 0.0005$), disease control rate (OR = 4.72, 95%CI: 1.75-12.72, $I^2 = 56\%$, $P = 0.002$), 1-year overall survival (OR = 3.10, 95%CI: 2.22-4.33, $I^2 = 41\%$, $P = 0.00001$), but further randomized trials are still ongoing with the aim to evaluate the effectiveness of this combination therapy (NCT01004978, NCT01324076, NCT01217034).

To develop novel systemic therapies for HCC, sorafenib was also evaluated as second-line therapy after fluoropyrimidine plus platinum-based chemotherapy[33]: The resulting disease control rate of 58.3%, with overall survival and progression-free survival of 7.1 and 2.3 mo, respectively, without increased incidence of adverse events, suggests a modest efficacy of sorafenib as second-line treatment after other systemic therapies. In consideration of new systemic therapeutic options, great importance has acquired the search for markers of resistance to sorafenib, with the intention to offer a personalized therapy for advanced HCC. An example is represented by c-Jun N-terminal kinase activity, related with the CD133 expression level and inversely correlated with the therapeutic response to the drug[8,34]. Thus, many efforts should be done to identify other markers of poor response to sorafenib, with the aim to give each patient a personalized therapeutic approach, based on the resistance profile of each single HCC and to choose among other drugs that will be hopefully soon available beside Sorafenib.

Brivanib

Brivanib is a small molecule acting as dual tyrosine kinase inhibitor (TKI) of VEGFR and FGFR. The drug, administrated orally (800 mg once daily), was initially evaluated as first line treatment in comparison with sorafenib in the BRISK-FL trial, then as second line treatment in comparison with placebo in patients who complained intolerance or lack of response to sorafenib in BRISK-PS trial. BRISK-FL trial[35] showed no difference regarding overall survival between brivanib and sorafenib (9.5 mo *vs* 9.9 mo, HR = 1.06, 95%CI: 0.93-1.22, *P* = 0.311). Even as second-line therapy, in comparison with BSC, Brivanib failed: BRISK-PS[36] trial showed no significant difference regarding overall survival between the two approaches (9.4 mo *vs* 8.2 mo, *P* = 0.3307). Finally, brivanib, like sorafenib, was tested in a randomized, double-blind, placebo-controlled trial[37] as adjuvant therapy after TACE in comparison with placebo, but even in this case it failed in improving overall survival of HCC patients (19.1 mo *vs* 26.1 mo, *P* = 0.5280). Thus, at this time evidences do not allow to consider brivanib an effective alternative to Sorafenib, but further studies may show better results, if we consider positive data about time to tumor progression (4.2 mo *vs* 2.7 mo; HR 0.56, 95%CI: 0.42-0.76, *P* < 0.001) from BRISK-PS and lack of cross tolerance with Sorafenib.

Sunitinib

Sunitinib is another small molecule acting as multikinase inhibitor which targets VEGFR, PDGFR and c-kit. Only one phase Ⅲ trial (SUN1170 trial)[38] studied the efficacy of the drug as first-line treatment for HCC, but was discontinued due to adverse events. Anyway sunitinib appeared to be inferior to sorafenib regarding overall survival (7.9 mo *vs* 10.2 mo, *P* = 0.0014). Based on current evidence, sunitinib is not to be considered as a viable therapeutic alternative to sorafenib.

Linifanib

Linifanib is a dual tyrosine-kinase inhibitor targeting VEGFR and PDGFR. LIGHT phase Ⅲ trial[39] compared the drug to sorafenib as first-line treatment, but overall survival between the two groups was similar (95%CI: 8.3-11.0, HR = 1.046, 95%CI: 0.896-1.221) and linifanib group showed higher rate of adverse events (*e.g.*, hypertension and hepatic encephalopathy).

Erlotinib

Erlotinib is a tyrosine kinase inhibitor targeting EGFR, which was evaluated in combination with sorafenib *vs* sorafenib alone in SEARCH phase Ⅲ trial[40]. This combination did not lead to an increased overall survival (9.5 mo *vs* 8.5 mo, *P* = 0.408) and was related to potent toxicity.

Everolimus

Everolimus acts inhibiting the mammalian target of rapamycin (mTOR). It was evaluated in comparison with placebo in EVOLVE-1 phase Ⅲ trial[41] in case of sorafenib failure or intolerance, but it did not increase overall survival (7.6 *vs* 7.3, HR = 1.05, 95%CI: 0.86-1.27, *P* = 0.68).

Ramucirumab

Ramucirumab is a recombinant IgG1 monoclonal antibody able to bind extracellular domain of VEGFR-2. REACH trial[42] failed in showing its efficacy as second-line treatment in comparison with placebo, because overall survival was similar between the two groups (9.2 mo *vs* 7.6 mo; HR = 0.87, 95%CI: 0.72-1.05, *P* = 0.14); however the promising results obtained in patients with alpha-fetoprotein > 400 ng/mL, led to an ongoing trial to verify its usefulness of this drug in this specific population.

Regorafenib

Regorafenib is a multi-target inhibitor acting on VEGFR1-3, TIE2, c-kit, Ret, wild type or V600-mutated B-RAF, PDGFR and FGFR, administered orally and derived from sorafenib. RESORCE[43] trial is a phase Ⅲ randomized, double-blind trial, that recently evaluated the drug as second-line treatment in comparison with placebo in patients who showed intolerance or failure to sorafenib. Regorafenib was related to positive results in terms of overall survival (10.6 mo *vs* 7.8 mo; HR = 0.63, 95%CI: 0.50-0.79, *P* < 0.0001). Adverse events reported are hypertension (15%), fatigue (9%), diarrhea (3%). It is possible to affirm, on the basis of this trial, that regorafenib appears to be the only alternative currently available regarding systemic therapy for the treatment of advanced HCC in case of progression on sorafenib treatment.

Other small molecules

Other small molecules are currently under evaluation for the treatment of HCC. Some of them act against targets already mentioned as factors involved in angiogenesis (*e.g.*, VEGF), other drugs act on pathways that are already targets of other drugs (*e.g.*, MEK, MET). It is important to emphasize that drugs that act on c-MET may have greater efficacy in cases of HCC with increased expression of the receptor[44,45]. Phase Ⅲ studies are required to define the clinical utility of these drugs, in particular in comparison with sorafenib; for some of them phase Ⅲ trial are under way. Table 1 shows a list of drugs under preliminary evaluation.

CYTOTOXIC CHEMOTHERAPY

Historically, traditional chemotherapy agents have not shown great efficacy in the treatment of HCC when used in advanced stage of disease, in particular in case of progression after locoregional therapy. This assessment comes from initial examination of single-arm, open-label studies evaluating the use of some chemotherapeutic, that did not lead in the past years to further evaluation

Table 1 Targeted drugs under evaluation in advanced hepatocellular carcinoma

Drug	Molecular target	Study design	DCR	PFS	OS	TTP	Tolerabilty	Phase III study
Lenvatinib[46]	VEGFR, FGFR, PDGFR,RET, KIT	Phase I/II (first line)	NR	NR	18.7 mo	12.8 mo	Favorable profile	Ongoing (E7080)
Cabozantinib[47]	VEGFR-2, MET, RET	Phase II (second line)	68% at 12 wk	4.2 mo	NR	NR	Favorable profile	Ongoing (NCT01908426 – CELESTIAL)
Tivantinib[48]	c-MET	Phase II (*vs* placebo, second line)	MET low NS MET high 50% *vs* 20%	NR	MET low NS MET high 7.2 mo *vs* 3.8 mo; $P = 0.01$	MET low NS MET high 2.7 mo *vs* 1.4 mo; $P = 0.04$	Severe neutropenia	Ongoing (NCT01755767)
Apatinib[49]	VEGFR2	Phase II (first line)	NR	NR	9.7 mo	4.2 mo	Favorable profile	Ongoing (NCT02329860)
Refametinib[50]	MEK	Phase II (+ sorafenib)	43%[1]	NR	290 d[1]	122 d[1]	High incidence of 3/4 grade adverse events	NR
Foretinib[51]	MET, RON, AXL, TIE-2, VEGFR	Phase I/II (first line)	79%	NR	NR	4.2 mo	Favorable profile	NR
Tepotinib[52]	c-MET	Phase Ib/II (*vs* sorafenib, first line) - Ongoing	NR	NR	NR	NR	Favorable profile	NR
Capmatinib[53]	c-MET	Phase I	NR	NR	NR	NR	Favorable profile	NR
Golvantinib[54]	c-MET	Phase I/IIb (+ sorafenib) - Ongoing	NR	NR	NR	NR	Favorable profile	NR
Emibetuzumab[55]	c-MET	Phase I (monotp *vs* emibetuzumab + erlotinib)	NR	NR	NR	NR	Favorable profile	NR
LY2157299[56]	TGF-β	Phase II (second-line)	NR	NR	36 wk[2]	12 wk[2]	Favorable profile	Ongoing
Pazopanib[57]	VEGFR1-3, PDGFRα-β, c-kit	Phase I	NR	NR	NR	NR	Favorable profile	NR
Axitinib[58]	VEGFR1-3	Phase II (*vs* placebo, second line)	NR	3.6 mo *vs* 1.9 mo; $P = 0.004$	12.7 mo *vs* 9.7 mo; $P = 0.287$	3.7 mo *vs* 1.9 mo; $P = 0.006$	Acceptable profile	NR

[1]Best clinical response was observed in case of RAS mutations; [2]Best clinical response was observed in case of AFP level decrease. DCR: Disease control rate; OS: Overall survival; TTP: Time-to-tumor progression; PFS: Progression free survival; NR: Not reported; NS: Not significant.

of this class of drugs and limiting their use to palliative approaches.

Recently, however, new chemotherapeutic agents, such as oxaliplatin, have shown efficacy in the treatment of cancers of the digestive tract (stomach, colorectal, pancreas). Based on these positive results, some of these drugs have also been evaluated for the treatment of advanced HCC, with promising findings.

Monotherapy regimens

This kind of regimen is indicated in case of worse general conditions or worse tolerance to systemic therapy. Doxorubicin was one of the first chemotherapic drugs used for HCC and showed interesting results[59], but its role is actually related to already mentioned DEB-TACE. Doxorubicin was also evaluated in combination with sorafenib (see below for details). The interest for doxorubicin is growing again due to the technological advance that allows a targeted release of the drug; this aspect will be discussed in another section of this review. Capecitabine is a drug converted to 5-fluorouracil (5-FU) which acts on DNA synthesis, slowing tumor growth. Currently its role in HCC treatment regards adjuvant therapy after surgery, based on a randomized, controlled trial, placebo-controlled[60], that showed lower recurrence rate (53.3% *vs* 76.7%) and higher time-to-tumor progression (40 mo *vs* 20 mo, $P = 0.0046$); 5-years-overall survival was better in capecitabine group, even if this result did not reach statistical significance (62.5% *vs* 39.8%, $P = 0.216$). From a point of view of safety profile, the drug showed a good tolerability. TS-1 (Titanium-silicate) is a newly developed chemotherapeutic agent that acts on metabolism of 5-FU, increasing its toxicity in neoplastic

cells. Its effect was observed for the treatment of other GI tumors, so it was evaluated as second line treatment for HCC in comparison with placebo in a phase Ⅲ trial (S-CUBE)[61]. This trial failed in proving the superiority of this drug over placebo, but a subanalysis[62] suggests that better results could be observed in a more specific population, characterized by TNM stage Ⅲ, Ⅳa or IVb, Child-Pugh liver function class A and low levels of tumor markers. In this subgroup, overall survival was significantly longer (426.0 d *vs* 375.5 d; HR = 0.69; 95%CI: 0.51-0.93, *P* = 0.0156), suggesting that more personalization in therapeutic approach should be aimed. Nonetheless this studies show how the best possible results for the systemic therapy are linked to good liver function and to a not too advanced disease.

Politherapy regimens

As previously said, newly developed chemotherapeutic agents, appear to be a valuable option for HCC. FOLFOX4 regimen (fluorouracil, leucovorin, oxaliplatin) was evaluated in comparison to doxorubicin alone for the treatment of advanced HCC ineligible for surgery or for local treatments in EACH trial (phase Ⅲ trial)[63]. FOLFOX4 was related to better results in terms of progression free survival (2.93 mo *vs* 1.77 mo, *P* < 0.001), response rate (8.15% *vs* 2.67%, *P* = 0.002), disease control rate (52.17% *vs* 31.55%, *P* < 0.001); beside these positive findings and a good safety profile, no significant difference in terms of overall survival, the primary endpoint of the study, was observed (6.40 mo *vs* 4.97 mo, *P* = 0.07), leading to a formal negativity of the study. Still, an unplanned subsequent analysis performed at 7 mo after the end of the previous study has shown an improvement in terms of overall survival (6.47 mo *vs* 4.90 mo, *P* = 0.04) and significant results regarding overall survival (5.9 mo *vs* 4.3 mo, *P* = 0.0281), but progression free survival, response rate and disease rate control in the Chinese population[64], leading to FOLFOX4 approval by Chines Food and Drug Administration for treatment of advanced HCC ineligible for surgery or local treatment. GEMOX regimen (gemcitabine, oxaliplatin) was firstly evaluated in a large, multicenter, retrospective study (AGEO)[65] for treatment of advanced HCC with notable results: 22% response rate, 66% disease control rate, 4.5 mo progression free survival, 8.0 mo time-to-tumor progression and 11.0 mo of overall survival. Two interesting aspects should be considered: As first, overall survival was related to cirrhosis stage and response to the regimen were associated to overall survival; in particular response to GEMOX led to a better overall survival in comparison with lack of response (19.9 mo *vs* 8.5 mo). As second, this regimen was related to a downstaging effect on the neoplasia, considering that 8.5% of patients became eligible for curative-intent treatments. Attention should be given to possible serious side effects of this regimen (neurotoxicity, thrombocytopenia, neutropenia and diarrhea). Another retrospective study[66] subsequently evaluated GEMOX as second-line treatment after failure of targeted therapy, reporting an overall survival of 8.3 mo, a 6-mo overall survival rate of 59% and a progression free survival of 3.1 mo. Even this study showed an association between overall survival and performance status, alpha-fetoprotein and BCLC score at diagnosis. Further studies are therefore required, in particular phase 3 trials, to assess the role of this regimen in the treatment of HCC. Some other oxaliplatin-based regimens have begun to be studied in phase Ⅱ trials for HCC treatment, showing interesting results, such as XELOX[67] (oxaliplatin plus capecitabine), GP[68] (gemcitabine plus cisplatin) and cisplatin plus capecitabine[69]. A meta-analysis study[70] tried to define the efficacy and safety of oxaliplatin-based regimens and to assess the best regimen for treatment of advanced HCC, but it as an important limitation having evaluated only small single arm studies, with the exception of the EACH study; anyway, it suggests that better results could be obtained with GEMOX combination. Given the yet ambiguous and preliminary available data, further efforts are necessary, performing randomized trials on extended samples, to define the role of these regimens for treatment of HCC.

Chemotherapy and sorafenib

The growing interest about chemotherapy for the treatment of HCC, has led to its comparison with the only available standard systemic treatment: Sorafenib.

As previously said, there are no significant data about comparison between sorafenib and chemotherapeutic drugs, being the lack of phase Ⅲ randomized trials a reason. As a matter of fact, this comparison was evaluated only retrospectively[71] with no significant difference in overall survival (23 wk *vs* 43.6 wk, *P* = 0.105) and progression free survival (11.1 wk *vs* 12.4 wk, *P* = 0.496). More efforts were done to assess a possible synergistic effect of sorafenib plus chemotherapeutic agents. After initial promising data from a phase Ⅱ study[72], a phase Ⅲ trial (CALGB80802)[73] was planned to assess the efficacy of doxorubicin plus sorafenib in comparison with sorafenib alone as first-line treatment, but it was interrupted after a planned interim analysis demonstrated a higher toxicity in combination group and because primary and secondary endpoints (overall survival and progression free survival, respectively) were not met. The main difference between this and the previous phase Ⅱ trial is represented by the use of sorafenib in the control group instead of doxorubicin, suggesting that sorafenib could be the determinant in the therapeutic effect of this combination, with a marginal role of doxorubicin. The GONEXT study[74], a phase Ⅱ study, evaluated the combination of GEMOX plus sorafenib *vs* sorafenib alone as first-line therapy, with moderately positive results: Response rate (16%), disease control rate (77%), median progression free survival (6.2 mo) e 4-mo progression free survival rate (61%), even if overall survival was similar to the

one reported for sorafenib monotherapy; tolerability resulted to be acceptable. The authors commented results pointing out that primary endpoint was met (4-mo progression free survival > 50%), while other results were encouraging. Another preliminary randomized study[75] evaluated this combination as first-line treatment (6 cycles) followed by maintenance treatment with sorafenib alone: objective response was 26.5%. The median time to progression was 10.3 mo (95%CI: 8.7-11.9 mo) and median overall survival was 15.7 mo (95%CI: 13.0-18.4 mo). Toxicity was manageable. Even this approach deserves further evaluations with phase Ⅱ and Ⅲ trials. Another phase-Ⅱ trial[76] studied SECOX regimen (sorafenib, capecitabine and oxaliplatin) in Asian HCC patients; the primary endpoint was time-to-tumor progression (5.29 mo), while secondary ones were response rate (16%), progression free survival (5.26 mo), overall survival (11.73 mo) and tolerance (good tolerance). Results were thus considerate promising and deserving of further evaluations. It is therefore possible to state that oxaliplatin based regimens plus sorafenib showed results suggesting a synergistic action between these drugs and a possible fundamental role in the future of treatment of HCC.

HAIC

HAIC was introduced in Japan before the advent of sorafenib and Japanese clinical guidelines suggested HAIC plus sorafenib in case of HCC with Vp4 or Vp3 (HCC with invasion of the main trunk or the left and right main branches of the portal vein) even in absence of phase Ⅲ trials supporting the efficacy of this approach. Available regimens are: IA-call (one-shot intra-arterial injection), LFP (repeated intra-arterial injection of cisplatin with a reservoir catheter system) and 5FU/IFN (5-fluorouracil continuous intra-arterial injection with a reservoir catheter system in combination with subcutaneous interferon administration). The best results from a single regimen came from IA-call, that was related to a response rate of 33.8% in a phase Ⅱ trial[77]. As previously said, these regimens are often used in combination with sorafenib, but only combination based on IA-call was associated to interesting results in terms of overall survival in comparison with sorafenib alone (9.5 mo *vs* 7.0 mo; HR = 0.74)[78]. On the other side, no significant difference was observed using sorafenib+LFP (11.8 mo *vs* 11.8 mo; HR = 1.0)[79].

IMMUNOTHERAPY

Tumor immune escape ad its mechanism brought to a growing interest from scientific community, resulting in development of tumor immunotherapy, that proved to be effective for the treatment of some malignant neoplasia (*e.g.*, melanoma, NSC lung cancer, renal carcinoma). Two immunological pathways are involved in tumor immunotherapy: The first one is related to T cells inhibition caused by the interaction between cytotoxic T lymphocyte-associated-4 (CTLA-4), a transmembrane receptor on T cells, and its molecular ligand B7, that may lead to a protective effect for tumor cells and its inhibition is the target of some immunotherapeutic drugs[80]. The second immunological pathway targeted by immunotherapy is the one started by programmed death receptor 1 (PD-1) and its ligands (PD-L1 and PD-L2). PD-1 is produced by several immunity cells (T cells $CD28^+/CD4^+$, B cells, NK cells, *etc*.) but it's often expressed by tumor cells with an immunosuppressive effect, caused by TCR receptor signal transduction inhibition by PD-1-PD-L1 that results in drop of proliferation and depletion of T-cells[81]. Tremelimumab is a humanized anti-CTLA-4 IgG2 antibody and it was evaluated for the treatment of HCC in patients with chronic HCV infection with encouraging results in terms of response rate (18%), disease control rate (76%) and time-to-tumor progression (6.48 mo); two interesting characteristics of this drug are its long half-life (22 d), which could lead to a more comfortable management for the patient, and its antiviral activity, represented by a drop in viral load[82]. An interesting important clinical aspect is the possible synergistic action of this drug with local treatments (TACE and RFA). This synergy might be explained by immune reaction against the tumor caused by local treatments, which improves the efficacy of immunotherapeutic drug. Only preliminary results[83] are available, but they appear to be promising: 40% of patients reached partial response, 5/7 patients affected by HCV infection showed a drop in viral load, histology evaluation showed immune cell infiltration in tumor and progression free-survival was 7.4 mo; in addition no worsening of safety profile was observed. Nivolumab is a fully humanized monoclonal IgG4 antibody against PD-1, recently studied in a phase Ⅰ/Ⅱ study[84] for treatment of patients affected by HCC with intolerance to, or inefficacy of, sorafenib. This study reported extremely positive results: 2/39 patients (5%) showed complete response and 8/39 (18%) showed partial response; 6-mo overall survival rate was 72%. On the other hand a moderate rate of adverse events was observed (71%), but only 17% of patients were affected by grade 3/4 adverse events (elevated AST, elevated ALT, elevated serum lipase). A phase Ⅲ trial (NCT02576509) to compare nivolumab to sorafenib is ongoing. It is safe to say that tumor immunotherapy is a very promising option among systemic therapies, especially because its targets are completely different from targets of the currently available systemic therapies. Furthermore, its effectiveness may allow a better understanding of the biology of HCC. In the near future it will be interesting to evaluate immunotherapy in comparison with standard treatments, but also in combination with them in consideration of possible synergy as seen in case of Tremelimumab and TACE.

FUTURE PERSPECTIVES

HCC appears to be still a tough opponent, if it is not possible to treat it by surgery or by transplantation. It this therefore necessary to improve medical therapy for this neoplasia to give a chance to patients affected by its more advanced stages. It is important to focus which are directions we should follow regarding research in this field.

Understanding why some drugs had partial results or were able to show improvements only in some groups of patients is very important and could allow us to understand resistance mechanisms of this neoplasia and to develop strategies to overcome them. On the other side, many efforts should be made to find new therapeutic targets and develop new drugs. Certainly, the future of advanced HCC treatment will be represented by personalized therapy based on a deep evaluation of the patients, to find out the better targets of disease to be attacked.

Resistance mechanisms

Not so much data is available about resistance mechanisms of HCC and practical ways to overcome them. Preliminary studies have shown that, as previously said, c-Jun N-terminal kinase activity could be related to sorafenib resistance, but this information did not lead to clinical consequences yet. Resistance could be related to systemic therapy in general or to the single drug. In the first case, altered pathways are fundamental for tumorigenesis, metastatic process and maintenance of stem cell properties; in particular molecules involved in autophagy (osteopontin[85]), apoptosis (Cofilin-1[86] and AKR7A3[87]) and stemness related mechanism of cancer stem stells (NRBP2[88]) seem to play an important role, as showed in some preliminary *in vitro* studies.

Particular mechanisms resulted to be involved in resistance to specific drugs. For example, aberrant expression of non-coding RNA was related to oxaliplatin-resistant profile: 421 differentially expressed mRNAs, 228 up-regulated and 193 down-regulated (fold change > 2, $P < 0.05$) in oxaliplatin-resistant (MHCC97H-OXA), were individuated and appear to be related not only to resistance to oxaliplatin, but also to tumor size, differentiation and poor prognosis[89]. On the other hand, TUC338\RASAL1 pathway was related by Jin *et al*[90] to sorafenib resistance: *in vitro* inhibition by non-coding RNA of TUC338 led to a sensitization to sorafenib and, in addition, to a decrease in proliferative and invasive ability. Of particular interest is the recent hypothesis of the role of tumoral microenvironment in chemotherapeutic resistance: Azzariti *et al*[91] described in their study the resistance to sorafenib induced by hepatic stellate cells, that produce laminin-332, an extracellular matrix protein, that is able to bind α3β1 integrin, if expressed, leading to protection of FAK, a target of sorafenib, from degradation.

New combinations of drug with delivery systems or biological enhancers

Another important field of research is the one regarding the development of new forms of drugs already used to enhance the effect and selectivity for HCC; an example is represented by nanoparticle-mediated targeted drug delivery system[92]. Doxorubicin is an example of drug that could soon have a new role in HCC treatment, as demonstrated by preliminary studies on animal models with modified forms of the drug. Lactosaminated albumin conjugate of doxorubicin showed rapid and selective accumulation in the liver[93], such as mesoporous magnetic nanocomposites wrapped with chitosan gatekeepers[94], that in addition exploit acidic pH of tumoral cells with a selective release of drug at pH 4.0. Even A54 peptide modified Doxorubicin glucolipid conjugate micelles[95] showed high selectivity for hepatic cells, in particular for tumoral ones because of redox-sensitivity.

Moreover the modification of cisplatin by the addition of a pH-sensitive polymer and HCC-targeting peptide, to obtain a higher selectivity to HCC and in particular to its stem cells, that are not sensitive to cisplatin alone, showed promising results[96]. On the other hand, elaboration of sorafenib was targeted to add molecules which could acts as biological enhancers in a synergistic way. Two examples of molecules used with this intent are C2-ceramide[97], a potent inducer of apoptosis in human neoplastic cells, and 2-Deoxyglucose[98], an inhibitor of glycolysis that leads to depletion of ATP.

Other drugs under evaluation

Pre-existing and new drugs were studied for treatment of HCC. Antiangiogenic drugs could have a role, because of important angiogenic activity of this neoplasia; in fact VEGFR is already a target of some drugs previously discussed. Unfortunately, bevacizumab was tested in combination with sorafenib in a phase I/II trial with consequent observation of high toxicity and low efficacy of this combination, that led to the interruption of the study[99,100]. It's necessary to mention drugs that have been studied *in vitro* and *in vivo* with promising results, awaiting for trials on humans. Some examples are ursolic acid derivates[101] and a B5G9[102] (piperazidine derivative of 23-hydroxy betulinic acid), that cause ROS-mediated apoptosis in HCC cells, EMMQ[103] (an indolylquinoline derivative), that causes DNA damage by activating p53 and γ-H2AX, and GL63[104] (a curcumine analogue), which was able to suppress the proliferation of HCC cells by inhibition of the JAK2/STAT3 signaling pathway. Even Valproic Acid[105], a well-known antiepileptic drug, showed potential anti-HCC effect *in vitro* by promotion of epithelial mesenchymal transition of hepatocarcinoma cells *via* transcriptional and post-transcriptional up regulation of Snail.

Another new therapeutic approach regards arginine, which cannot be produced by HCC cells; thus, pegy-

lated arginine diminase (ADI-PEG 20) was tested as arginine-degrading enzyme, with favorable tolerability[106] and encouraging disease control rate and median overall survival[107]; a phase Ⅲ trial to evaluate this drug is actually ongoing (NCT01287585). JX-594 is a recombinant vaccine virus able to cause virus replication-dependent oncolysis and tumor-specific immunity, after inserting human granulocyte-macrofaghe colony-stimulating factor (hGM-CSF) and β-galactosidase transgenes, with disruption of the viral thymidine kinase gene. This vaccine was tested in a low dose administration *vs* a high dose administration; this last one was related to a better median overall survival (6.7 mo *vs* 14.1 mo; HR = 0.39, *P* = 0.02), while response rate was 15% for both groups[108]. PHOCUS phase Ⅲ trial in combination with sorafenib is ongoing (NCT02562755).

New molecular targets

The advancement of knowledge of the biology of HCC is gradually allowing us to identify new potential molecular targets, which are an essential part of the development and the activity of this tumor. Rao *et al*[109] recently provided an article in which frequently mutated genes/pathways are described and can be source of inspiration to individuate new future therapeutic targets.

NF-κB has a key role in immune response and resulted to be altered in precancerous cirrhosis tissues and in a subset of HCCs. Ramesh *et al*[110] reported preliminary data about *in vitro* activity of ornithogalum against HCC. The importance of NF-κB in HCC biology and in relation to a potential clinical use, was suggested by Chen *et al*[111]: In his study, pretreatment of sorafenib with RT suppressed the expressions of NF-κB and its downstream proteins induced by radiation through downregulation of phosphorylated extracellular signal-regulated kinase (pERK), with a synergistic effect that could lead to a new role for radiotherapy for the treatment of HCC. Another target that has been evaluated in oncology is telomerase, which appears to be constitutively activated in many tumors. In a recent review by Picariello *et al*[112], inhibition of telomerase activity were evaluated. An interesting new approach is the exploitation of telomerase activity using nucleoside analogues that could be metabolized by telomerase. Acycloguanosyl-thymidyltriphosphate[113], a thymidine analogue pro-drug of Acyclovir, was tested *in vitro* and *in vivo* against HCC, leading to reduced tumor growth, increased apoptosis and reduced proliferation of tumor cells in transgenic and orthotopic mouse models. Further studies are necessary to test this kind of drugs on humans.

Other promising molecular targets are prothymosin-alpha[114], a negative regulator of apoptosis, *NEK2*[115], a critical regulator of centrosome structure and function, and *STARD13*[116], a positive regulator of apoptosis.

CONCLUSION

To date, the treatment of HCC is still a major surgical and medical challenge. This is even more true with regard to cases of advanced disease, treatable only with systemic therapy, which by now has few arrows available in its quiver. Sorafenib is today the only standard systemic treatment, but it presents still unsolved issues; this explains the urgency of finding new alternatives to be proposed to the patient. Molecular therapy has a key role: Many drugs are under development and under evaluation; furthermore another drug from this class, Regorafenib, showed positive results and for sure will be considered by future guidelines for the treatment of HCC; on the other hand, the number of available drugs is likely to increase with the rise of biological weaknesses of this neoplasia. Yet, cytotoxic drugs, in particular modified forms, and immunotherapeutic drugs are making a promising competition to sorafenib, acting on different routes. The future availability of a great number of different options with different mechanisms of action definitely gives much hope regarding the treatment of advanced HCC, in particular in terms of personalized therapy.

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MINIREVIEWS

Is the 25-year hepatitis C marathon coming to an end to declare victory?

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Abstract

Hepatitis C virus (HCV) which was originally recognized as posttransfusion non-A, non-B hepatitis has been a major global health problem affecting 3% of the world population. Interferon/peginterferon and ribavirin combination therapy was the backbone of chronic HCV therapy for two decades of the journey. However, the interferon based treatment success rate was around 50% with many side effects. Many chronic HCV patients with psychiatric diseases, or even cytopenias, were ineligible for HCV treatment. Now, we no longer need any injectable medicine. New direct-acting antiviral agents against HCV allowed the advance of interferon-free and ribavirin-free oral regimens with high rates of response and tolerability. The cost of the medications should not be a barrier to their access in certain parts of the world. While we are getting closer, we should still focus on preventing the spread of the disease, screening and delivering the cure globally to those in need. In the near future, development of an effective vaccine against HCV would make it possible to eradicate HCV infection worldwide completely.

Key words: Treatment; Therapy; Epidemiology; History; Prevention

Core tip: Spreading awareness about the need for screening and treatment of hepatitis C virus (HCV) will help identifying more cases to provide appropriate treatment. As more direct-acting agents are coming out of the pipeline, healthcare managers will face the major task of making those medicines available to HCV-infected patients. One of the efforts, successfully dismantling some of those barriers is the Extended Community Healthcare Outcomes project. Finally, efforts toward developing effective vaccines should be boosted as history tells us that most of success stories in eradicating infectious illness were made possible largely because of vaccines against the offending pathogen.

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INTRODUCTION

It has been less than three decades since the discovery of hepatitis C virus (HCV) in 1989 by Choo *et al*[1]. The process of discovering the virus was very daunting as described in Dr. Houghton's paper[2]. Recognized as the reason behind non-A non-B hepatitis, the big picture of the health and financial burden this virus would have caused became clear. With the high sustained virologic responses (SVRs) reported recently with the use of direct acting, soon will be forgotten the miserable quality of life patients of hepatitis C have had to endure with the not as effective and with unpleasant side effects interferon-based treatments. Not until five years ago when direct acting agents, protease inhibitors telaprevir (Incivec, Vertex) and boceprevir (Victrelis, Merck) were approved by the Food and Drug Administration, had we started seeing SVR rates above 70%. Since then, many direct acting agents have been approved with SVR rates above 90%. While very promising, challenges for treatment, such as access to medications and healthcare management, remain widely spread.

NATURAL HISTORY OF HEPATITIS C

After the acute infection, only 15%-25% of the patients get cured spontaneously and 75%-85% develop chronic infection with the diagnosis made if viremia persists 6 mo from the onset. Chronic inflammation will lead eventually to structural damage or fibrosis which, as it progresses, will lead to cirrhosis. From those chronically infected, 10% to 15% develop cirrhosis[3]. Progression of fibrosis can be influenced by host factors [such as older age at time of infection, male gender, coinfection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), immunosuppression, insulin resistance, non-alcoholic steatohepatitis, hemochromatosis, schistosomiasis, and the grade and stage on the liver biopsy] as well as external factors (such as excessive alcohol drinking). HCV and HBV play an etiologic role in acute liver failure[4]. HCV has mostly a dominant role in HBV and HCV coinfection[5]. However, HBV acute superinfection may cause spontaneous clearance of HCV RNA[6].

Liver biopsy remains the gold standard for the grading and staging of chronic hepatitis C. The grade, which reflects the inflammation activity, is determined by the severity of mononuclear inflammatory cells around the portal areas and by necrosis of the hepatocytes. The stage reflects the extent of the fibrosis which ranges from absent to mild or advanced in case of bridging fibrosis (fibrosis extending from a portal tract to another) or cirrhosis (fibrosis closing up in circles forming nodules).

Deaths usually are caused by complications of cirrhosis such as ascites, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, and hepatocellular carcinoma (HCC). Unfortunately, the disease can progress silently until it is advanced and complications ensue. For compensated cirrhosis, 3-, 5-, and 10-year survival rates were 96%, 91%, and 79%, respectively[7]. The 5-year survival rate drops to 50% once decompensated[7]. HCC risk increased 17-fold in HCV-infected patients[8]. This risk appears to have decreased in those with a sustained viral response rather than non-responders to interferon treatment[9]. The rates of progression to cirrhosis and HCC have been variable with a mean time to cirrhosis estimated at 20 years[3,10]. HCC can develop at a rate of 1% to 4% per year[11-14].

EPIDEMIOLOGY OF HEPATITIS C

The prevalence of HCV antibody in the United States is 1.6%[15]. In 1999-2002, the highest prevalence (4.3%) was in people 40 to 49 years of age[15] and two-thirds of those infected were born between 1945-1965. In 2007, HCV infection was associated with an estimated 15000 deaths in the United States[16]. This number has risen to 19695 in 2014 and this is now thought of as only a fraction of the actual number[17]. Decompensated chronic HCV is the most common indication for liver transplantation in the United States[18,19]. HCV and chronic kidney disease are associated. Hemodialysis patients have five time higher risk of chronic HCV infection compared to the healthy population. On the other hand, HCV has extrahepatic manifestations of cryoglobulinemia and glomerulonephritis[20]. Chronic hepatitis C is a leading cause of HCC[21]. The incidence of acute hepatitis C in the United States was estimated to be 180000 cases per year in the mid-1980s, but declined to approximately 30000 new cases per year in 1995[22], and to 16000 cases in 2009[23]. In a more recent surveillance, the incidence of acute hepatitis C in the United States has been on the rise since 2011. The estimated number on the actual new cases was 16500 in 2011 and has risen to 30500 in 2014[17].

SCREENING FOR HEPATITIS C

Because of the lack of symptoms in compensated disease and because 75% of patients chronically infected with hepatitis C are unaware of their infection[24], screening can help identify those infected before their disease progresses to a late stage. The United States Preventive Services Task Force has found

Table 1 Food and Drug Administration approved anti-hepatitis C virus tests[28]

Abbott HCV EIA 2.0	Abbott Laboratories, AbbottPark, IL	EIA (Manual)
ADVIA Centaur HCV	Siemens, Malvern, PA, United States	CIA (Automated)
ARCHITECT anti-HCV	Abbott Laboratories, AbbottPark, IL	CMIA (Automated)
AxSYM anti-HCV	Abbott Laboratories, AbbottPark, IL	MEIA (Automated)
OraQuick Rapid Test	OraSure Technologies,Bethlehem,PA	Immunochromatographic (Manual)
Ortho HCV Version 3.0 EIA	Ortho	EIA (Manual)
VITROS anti-HCV	Ortho	CIA (Automated)

Anti-HCV: HCV antibody; EIA: Enzyme immunoassay; CIA: Chemiluminescent immunoassay; MEIA: Microparticle enzyme immunoassay; CMIA: Chemiluminescent microparticle immunoassay.

Table 2 Milestones in the history of hepatitis C

1975	Non-A, non-B hepatitis was first described[36,37]
1989	Randomized controlled trials were carried out using interferon alpha to treat non-A, non-B hepatitis[38-40]
1989	HCV was identified[1]
1991	Ribavirin is used as a monotherapy for chronic hepatitis C[41,42]
1995	The combination of interferon alpha and ribavirin were tested[43,44]
1996	Hepatitis C serine protease structure was published[45]
1998	First randomized double-blind, placebo controlled study using recombinant interferon alpha alone or in combination with ribavirin[46,47]
1999	Structure of hepatitis C RNA-dependent RNA polymerase NS5B was identified[48,49]
2001	Pegylated interferon alpha and ribavirin were used in trials[50,51]
2005	Structure of NS5A was published[52]
2011	First direct acting agents: Protease inhibitors were used in combination with pegylated interferon and ribavirin to treat hepatitis C genotype 1[53,54]
2012	Pilot studies using combinations of direct-acting antiviral drugs without interferon[55]
2014	Several direct acting antiviral medications were released to the market to treat different hepatitis C genotypes with SVR exceeding 90% and with better tolerability

HCV: Hepatitis C virus; SVR: Sustained virologic response.

evidence that screening high risk population and one time screening of those born between 1945 and 1965 is of moderate benefit. The risk of stigmatization appeared small and, although there was evidence for harm from liver biopsy of 1% bleeding risk and < 0.2% death risk from liver biopsy, the use of liver biopsy to guide the management is becoming less. In light of the availability of effective antiviral agents that have rare and self-limited side effects, identifying patients with chronic hepatitis C and treating them is probably of benefit[25].

There is adequate evidence that anti-HCV antibody testing followed by confirmatory polymerase chain reaction testing accurately detects chronic HCV infection. The number needed to screen to identify 1 case of chronic hepatitis C in a high risk population, such as past or present injection drug use, sex with an injection drug user, or blood transfusion before 1992, is < 20 persons and anti-HCV antibody testing is associated with high sensitivity (> 90%)[26]. There is also evidence that different noninvasive tests have good diagnostic accuracy in detecting fibrosis[27].

IS THERE A VACCINE YET?

Unlike hepatitis A and B, no vaccine is available to protect against hepatitis C. The high variability among different strains and the fast rate at which mutations can develop made it very challenging to create an effective vaccine[28]. Several attempts are currently made to create a vaccine either by directing efforts at a relatively stable glycoprotein that is used by the virus to invade liver cells[28].

ASSAYS

Testing for hepatitis C has improved over the years. Anti-hepatitis C tests are accurate and with high sensitivity > 90% in high risk groups. The CDC recommends one of three immunoassays; two enzyme immunoassays (EIA) (Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois, and Ortho® HCV Version 3.0 ELISA, Ortho-Clinical Diagnostics, Raritan, New Jersey) and one enhanced chemiluminescence immunoassay (CIA) (Vitros® Anti-HCV assay, Ortho-Clinical Diagnostics, Raritan, New Jersey) for the initial screening[29]. The OraQuick test has been also approved by the FDA for the initial screening in 2011[30]. A reactive initial test should be followed by a confirmatory nucleic acid test where the plasma is tested to detect (qualitative) or detect and quantify (quantitative) hepatitis C RNA. If HCV RNA is detected, that indicates active hepatitis C infection. If HCV RNA is not detected, that indicates a false positive HCV antibody test or resolved infection[31]. A single step, combined RT-PCR technique can detect HCV RNA from extracted liver tissue[32]. Occult HCV cases have only positive HCV RNA in the hepatocytes, while their plasma HCV markers are all negative[33,34]. Table 1 shows FDA approved anti-HCV tests[35], Table 2 shows the milestones in the history of hepatitis C.

Table 3 American Association for the Study of Liver Diseases/Infectious Diseases Society of America Guideline Recommendations: Genotypes 1, 2, 3, 4, 5 and 6 hepatitis C virus[58]

HCV genotype	Cirrhosis	Prior Tx	Recommended regimen	Alternative regimen	Notes
1a	No		LDV/SOF 12 wk		
			DCV + SOF 12 wk		
			SMV + SOF 12 wk		
			SOF/VEL 12 wk		
			GZR/EBR 12 wk		NS5A RAVs absent
				GZR/EBR 16 wk + RBV	NS5A RAVs present
			OBV/PTV/RTV + DSV 12 wk + RBV		
1b	No		LDV/SOF 12 wk		
			DCV + SOF 12 wk		
			SMV + SOF 12 wk		
			SOF/VEL 12 wk		
			GZR/EBR 12 wk		
			OBV/PTV/RTV + DSV 12 wk		
1a	Compensated	Naive	LDV/SOF 12 wk		
				DCV + SOF 24 wk ± RBV	
				SMV + SOF 24 wk ± RBV	No Q80K
			SOF/VEL 12 wk		
			GZR/EBR 12 wk		NS5A RAVs absent
				GZR/EBR 16 wk + RBV	NS5A RAVs present
				OBV/PTV/RTV + DSV 24 wk +RBV	
1a	Compensated	PR exp	LDV/SOF 12 wk + RBV or 24 wk		
				DCV + SOF 24 wk ± RBV	
				SMV + SOF 24 wk ± RBV	No Q80K
			SOF/VEL 12 wk		
			GZR/EBR 12 wk		NS5A RAVs absent
				GZR/EBR 16 wk + RBV	NS5A RAVs present
				OBV/PTV/RTV + DSV 24 wk + RBV	
1b	Compensated	Naive	LDV/SOF 12 wk		
				DCV + SOF 24 wk ± RBV	
				SMV + SOF 24 wk ± RBV	
			SOF/VEL 12 wk		
			GZR/EBR 12 wk		
			OBV/PTV/RTV + DSV 12 wk		
1b	Compensated	PR exp	LDV/SOF 12 wk + RBV or 24 wk		
				DCV + SOF 24 wk ± RBV	
				SMV + SOF 24 wk ±- RBV	
			SOF/VEL 12 wk		
			GZR/EBR 12 wk		
			OBV/PTV/RTV + DSV 12 wk		
1a or 1b	Decompensated	Naive or exp	SOF/VEL 12 wk + RBV		Child-Pugh B or C
2	No	Naive	SOF/VEL 12 wk		
				SOF + DCV 12 wk	
2	No	PR exp	SOF/VEL 12 wk		
				SOF + DCV 12 wk	
2	No	SR exp	DCV + SOF 24 wk ± RBV		
			SOF/VEL 12 wk + RBV		
2	Compensated	Naive	SOF/VEL 12 wk		
				SOF + DCV 16-24 wk	
2	Compensated	PR exp	SOF/VEL 12 wk		
				SOF + DCV 16-24 wk	
2	Compensated	SR exp	DCV + SOF 24 wk ± RBV		
			SOF/VEL 12 wk + RBV		
2	Decompensated	Naive or exp	SOF/VEL 12 wk + WB RBV		Child-Pugh B or C
			DCV + SOF 12 wk + low initial dose RBV		Child-Pugh B or C
3	No	Naive	SOF + DCV 12 wk		
			SOF/VEL 12 wk		
3	No	PR exp	SOF + DCV 12 wk		
			SOF/VEL 12 wk		
3	No	SR exp	DCV + SOF 24 wk + RBV		
			SOF/VEL 12 wk + RBV		
3	Compensated	Naive	SOF/VEL 12 wk		

			SOF + DCV 24 wk ± RBV		
3	Compensated	PR exp	SOF/VEL 12 wk + RBV		
			SOF + DCV 24 wk + RBV		
3	Compensated	SR exp	SOF + DCV 24 wk + RBV		
			SOF/VEL 12 wk + RBV		
3	Decompensated	Naive or exp	SOF/VEL 12 wk + WB RBV		Child-Pugh B or C
			DCV+ SOF 12 wk + low initial dose RBV		Child-Pugh B or C
4	No cirrhosis or compensated	Naive	SOF/LDV 12 wk		
			OBV/PTV/RTV 12 wk + RBV		
			GRZ/EBV 12 wk		
			SOF/VEL 12 wk		
4	No	PR exp	SOF/LDV 12 wk		
			OBV/PTV/RTV 12 wk + RBV		
			GRZ/EBV 12 wk		Relapse
			GRZ/EBV 16 wk + RBV		Others
			SOF/VEL 12 wk		
4	Compensated	PR exp	SOF/LDV 12 wk + RBV	SOF/LDV 24 wk	
			OBV/PTV/RTV 12 wk + RBV		
			GRZ/EBV 12 wk		Relapse
			GRZ/EBV 16 wk + RBV		Others
			SOF/VEL 12 wk		
5 or 6	No cirrhosis or compensated	Naive or PR exp	SOF/LDV 12 wk		
			SOF/VEL 12 wk		

AASLD: American Association for the Study of Liver Diseases; DCV: Daclatasvir; DSV: Dasabuvir; EBR: Elbasvir; GT: Genotype; GZR: Grazoprevir; LDV: Ledipasvir; OBV: Ombitasvir; PR: Peginterferon/ribavirin; PTV: Paritaprevir; RAV: Resistance associated variant; RBV: Ribavirin; RTV: Ritonavir; SMV: Simeprevir; SOF: Sofosbuvir; VEL: Velpatasvir; WB: Weight-based; SR: Sofosbuvir/ribavirin; exp: Experienced; Tx: Treatment.

DIRECT ACTING AGENTS ERA

In 2011, telaprevir and boceprevir became available as the first direct acting antivirals for the treatment of chronic hepatitis C with variable SVRs for the different genotypes. While the use of the protease inhibitors was a great milestone in the journey of treating hepatitis C with SVRs above 70%, it had limiting factors, such as the need to use in combination with pegylated interferon and ribavirin, and their limitations in treating those with decompensated cirrhosis. Pegylated interferon and ribavirin have exerted their antiviral activities by modulating the host immunity rather than directly inhibiting the virus. With the better understanding of the HCV non-structural proteins, agents that inhibited those proteins have shown promise by directly disabling the life cycle of the virus.

To overcome those species with resistance against the various agents, combination therapy with agents attacking different vital functions became available. Several trials have been conducted with many drugs and combinations of drugs tested in patients with different genotypes and subtypes as well as groups who were treatment naive and those with experience. Defining cure by achieving SVR, defined as the absence of virus detection with an acceptable HCV RNA assay at 12 wk after the end of the treatment, therapy outcomes were compared in those with and without cirrhosis, and between those with and without disease decompensation. While some data is still lacking in different special groups, we are learning more about how to treat those with comorbidities such as coinfection with HIV, those with renal disease, pediatric[56], and liver transplant patients[34,57]. Most of the regimens available at this time are interferon - free regimens and all oral medications with very limited side effects and with SVRs > 85% and in many cases > 95%. Table 3 summarizes the latest recommendations for treating the different HCV genotypes in different groups of patients[58-67].

SO DID WE FIND THE IDEAL CURE?

With manufacturing highly potent medications, we may be winning a battle against hepatitis C, but are we winning the war? The challenge in eradicating the disease lies in delivering and administering those medications to the appropriate patients and ensure their compliance with the treatment and follow up. Patient access to the medications is limited by cost, lack of healthcare services, and ignorance. While the AASLD recommends treating everybody with chronic hepatitis C, third party payers may restrict treatment to those with advanced disease. Payers may also limit the choice of medications authorized. Many healthcare providers choose not to treat hepatitis C because of the perception that such treatment is complex or at least time and resources consuming. Some providers and insurers will decline those with ongoing illicit drug or alcohol use. Shortening the treatment period in selected cases can significantly reduce the cost[68]. Many patients, an estimated 75% of those infected, do not know they have the disease and, therefore, do not seek the appropriate care. While such hindrances have been there all along, the challenge seems to be shifting more towards

socioeconomic nature.

WHAT IS NEXT?

As more direct acting agents are coming out of the pipeline, healthcare managers will have to face the major task of making those medicines available to chronic hepatitis C patients. Spreading awareness about the need for screening and for treatment if infected not only in the population at large, but also among the healthcare providers, will help identifying more cases of infection and help provide those with the appropriate treatment[69]. One of the efforts, successfully dismantling some of those barriers is the Extended Community Healthcare Outcomes project. Launched in New Mexico in 1993, the project has grown to encompass several national and international hubs. These hubs provide healthcare providers with the appropriate educational and coaching resources to empower them with the knowledge and with the How-To guidance to treat patients in their communities where no specialized care is available. This project has helped many patients in rural areas to receive treatment without the need to travel out of their own towns[70,71]. The project provides healthcare providers with direct access to specialized knowledge and provides them with step-by-step coaching which helps in alleviating the misperceptions about the complexity of the treatment and, hence, recruiting more providers in the war against hepatitis C.

On the preventative front, efforts should be also directed towards studying the increasing incidence of hepatitis C acute infection to identify the newer trends behind this surge and to try to eliminate them. While treating acute hepatitis C infection is still not recommended, we may need to revisit the guidelines to facilitate earlier treatment, particularly now that we have highly potent medications with few tolerable side effects.

Finally, efforts toward developing effective vaccines should be boosted as history tells us that most of success stories in eradicating infectious illness were made possible largely because of vaccines against the offending pathogen.

CONCLUSION

While we are getting closer, it is still early to declare victory against hepatitis C. We are armed with better ammunition, but we need to do better job in developing strategies that not only deliver cure to those in need, but also prevents the spread of the disease by educating the population about the risk factors for contracting the disease and how to avoid them, identifying the undiagnosed, and providing early treatment to those in need.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Small for size syndrome difficult dilemma: Lessons from 10 years single centre experience in living donor liver transplantation

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Abstract

AIM

To analyze the incidence, risk factors, prevention, treatment and outcome of small for size syndrome (SFSS) after living donor liver transplantation (LDLT).

METHODS

Through-out more than 10 years: During the period from April 2003 to the end of 2013, 174 adult-to-adults LDLT (A-ALDLT) had been performed at National Liver Institute, Menoufiya University, Shibin Elkoom, Egypt. We collected the data of those patients to do this cohort study that is a single-institution retrospective analysis of a prospectively collected database analyzing the incidence, risk factors, prevention, treatment and outcome of SFSS in a period started from the end of 2013 to the end of 2015. The median period of follow-

up reached 40.50 m, range (0-144 m).

RESULTS

SFSS was diagnosed in 20 (11.5%) of our recipients. While extra-small graft [small for size graft (SFSG)], portal hypertension, steatosis and left lobe graft were significant predictors of SFSS in univariate analysis (P = 0.00, 0.04, 0.03, and 0.00 respectively); graft size was the only independent predictor of SFSS on multivariate analysis (P = 0.03). On the other hand, there was lower incidence of SFSS in patients with SFSG who underwent splenectomy [4/10 (40%) SFSS *vs* 3/7 (42.9%) no SFSS] but without statistical significance, However, there was none significant lower incidence of the syndrome in patients with right lobe (RL) graft when drainage of the right anterior and/or posterior liver sectors by middle hepatic vein, V5, V8, and/or right inferior vein was done [4/10 (28.6%) SFSS *vs* 52/152 (34.2%) no SFSS]. The 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients with SFSS were 30%, 30%, 25%, 25%, 25% and 25% respectively, while, the 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients without SFSS were 70.1%, 65.6%, 61.7%, 61%, 59.7%, and 59.7% respectively, with statistical significant difference (P = 0.00).

CONCLUSION

SFSG is the independent and main factor for occurrence of SFSS after A-ALDLT leading to poor outcome. However, the management of this catastrophe depends upon its prevention (*i.e.*, selecting graft with proper size, splenectomy to decrease portal venous inflow, and improving hepatic vein outflow by reconstructing large draining veins of the graft).

Key words: Living donor liver transplantation; Outcome after living donor liver transplantation; Small for size syndrome; Small for size graft; Portal inflow; Venous outflow

Core tip: Small for size syndrome (SFSS) was diagnosed in 20 (11.5%) of our recipients where, small for size dysfunction affected 16 of patients (80%) and small for size non function was present in four patients (20%). Regarding graft size in patients with SFSS; 10, 5 and 5 of patients had extra-small graft [small for size graft (SFSG), graft recipient weight ratio (GRWR) < 0.8], small graft (GRWR ⩾ 0.8 and < 1) and medium sized graft (GRWR ⩾ 1) respectively. Extra small graft (SFSG), portal hyper-perfusion, severe portal hypertension (PHTN), and venous outflow obstruction were the main direct causes of SFSS in 10 (50%), 3 (15%), 4 (20%), and 3 (15%) of patients respectively. While extra-small graft, PHTN, steatosis and left lobe graft were significant predictors of SFSS in univariate analysis, only graft size was independent predictor of SFSS on multivariate analysis. On the other hand, there was non-significant lower incidence of SFSS in patients with SFSG when splenectomy was done, furthermore, there was non-significant lower incidence of the syndrome in patients with right lobe graft when drainage of the right anterior and/or posterior liver sectors by middle hepatic vein, V5, V8, and/or right inferior vein was done. The SFSS related mortalities were recorded in 13/20 of patients (65%). The 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients with SFSS were 30%, 30%, 25%, 25%, 25% and 25% respectively, while, the 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients without SFSS were 70.1%, 65.6%, 61.7%, 61%, 59.7%, and 59.7% respectively, with statistical significant difference.

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INTRODUCTION

Living donor liver transplantation (LDLT) is acceptable management option for end-stage liver disease (ESLD) patients to overcome organ shortage and waiting list death. On the other hand, adult-to-adults LDLT (A-ALDLT) is affected by the so-called SFSG[1]. Until now, there is debate about the least volume of the graft required for A-ALDLT[2,3]. The volume of liver graft is determined by either graft recipient weight ratio (GRWR)[4], or the ratio of graft volume relative to standard liver volume of the recipient (GV/SLV); SFSG are those with a GRWR < 0.8% and/or those with a GV/SLV < 35%[2,3]. So, if GRWR < 0.8 % or a GV/SLV < 35%, the graft should be regarded as SFSG[5-8]. As SFSS occurrence depends upon the liver graft volume as well as other different negative factors, SFSG and SFSS definitions differ in different institutes and at different times[9,10].

SFSS diagnosis is determined by persistent elevation of bilirubin and large volume of ascites during the early period post liver transplantation (LT) with absence of other possible causes[2,3,11]. Generally, it is characterized by occurrence of the followings at the end of the 1st week post LT: Persistent cholestasis, coagulopathy, ascites, encephalopathy and/or bleeding from gastrointestinal tract and/or renal failure in some severe conditions[4,11-19]. Moreover, SFSS can be defined as Total bilirubin > 10 mg/dL and/or output of ascites > 1 L/d on the 14th day after LT[7].

The loss of balance between the rapid liver regeneration and the increased demand of liver to do his function is the principal pathogenesis of SFSS[3,20], moreover, it has become evident that SFSS is not just caused by SFSG, but by multiple factors. These factors are divided into graft-related factors and recipient

related ones[19,21-23].

The graft related factors include: (1) high portal inflow[17,20,24]; (2) low venous outflow[25,26]; (3) Pree-xisting steatosis in the donor[27,28]; (4) advanced donor age[29]; and (5) both warm and cold ischemia times[16,30,31]. However, recipient-related causes include severe preoperative ESLD and poor health status[7,16,32,33].

As occurrence of SFSS is determined by the balance between the functional mass of the liver, inflow of portal venous (PV), and outflow of hepatic vein (HV), Strategies to prevent it depend upon increasing the volume of liver graft and controlling adequate PV inflow and HV outflow by the surgical and the non-surgical techniques[22,34]. For increasing graft volume, a larger-sized graft, such as the right lobe (RL) graft, is used as the standard strategy for A-A LDLT to fulfill the required metabolic demands of adult recipients[35-38]. There are different techniques for control of graft inflow (*i.e*., splenectomy, splenic artery embolization, splenic artery ligation, mesocaval - or portocaval shunts)[39,40]. For outflow modulation; any short HV (especially RIV, V5, V8) larger than 0.5 cm are preserved, to be anastomosed with the recipient inferior vena cava (IVC)[3].

Splanchnic vasoconstrictors, intravenous octreotides, and oral propranolol may improve the persistent hyperbilirubinemia and coagulopathy in SFSS adult recipients[40,41]. The purpose of this work was to analyze the incidence, risk factors, prevention, treatment and outcome of SFSS after LDLT.

MATERIALS AND METHODS

Patients

Two hundred ten LDLT operations were done between April 2003 and December 2013 in our surgical department, National Liver Institute, Menoufiya university, our study included 174 adult patients after exclusion of cases with data loss and pediatrics, after taking the approval of our institutional reviewers (IRB); we did this cohort study which is a single-institution retrospective analysis of a prospectively collected database that analyzed the incidence, risk factors, prevention, treatment and outcome of SFSS in a period started from the end of 2013 to end of 2015, with patients observation from the 1st post-operative day (POD 1) until December 2015 or until patient death. The median period of follow-up reached 40.50 m, range (0-144 m).

The characteristics of recipients and their donors (including operative parameters): Regarding recipient gender, males were 154 (88.5%) while females were 20 (11.5%); furthermore, the mean age of them reached 46.5 ± 8.1 years. As regard donor gender, male donors were 118 (67.8%) and females were 56 (32.2%); the donors mean age reached 27.2 ± 6.7 years. According to Child-Pugh score, child A, B, and C were 9 (5.2%) 53 (30.5%) and 112 (64.4%) respectively, on the other hand, the mean model for end stage liver disease score(MELD) was 16.09 ± 4.3, moreover, MELD < 18, MELD 18-24, and MELD > 24 were 114 (65.5%), 50 (28.7%) and 10 (5.7%) respectively. Pre LT portal hypertension (PHTN) affected 144 (82.8%) of them.

Steatosis affected nine (5.2%) of grafts. The RL graft was given to 166 (95.4%) and the LL was given to 8 (4.6%) of them. The MHV was reconstructed in 17 (9.8%) of patients, furthermore, there were single, double, three and four HV anastomoses in 110 (63.2%), 53 (30.5%), 10 (5.7%) and 1 (0.6%) of them respectively. However, drainage of right anterior and/or posterior sectors by MHV, V5, V8, and/or RIV in RL grafts occurred in 56/166 (33.7%) of patients. The mean actual graft weight and actual GRWR were 820.9 ± 174.2 g and 1.04 ± 0.2 g respectively, moreover, SFSG (GRWR < 0.8) was found in 17 (9.8%) of patients, where splenectomy was done in seven (41.2%) of them to decrease portal hyper-flow. The decision to do intra-operative splenectomy was as follow: 4 cases due to severe pre transplant PHTN and SFSG (GRWR = 0.7, 0.73, 0.74, and 0.75) and the other 3 cases due to extra SFSG (GRWR = 0.57, 0.65, and 0.66).

Regarding cold ischemia and warm ischemia times, their mean reached 74.9 ± 51.2 min and 52.9 ± 15.2 min respectively. On the other hand, the mean intra-operative plasma and blood transfusion reached 8.2 ± 8.9 units and 7.05 ± 7.4 units respectively. Lastly, operative time mean was 13.1 ± 3.2 h while the in-hospital stay mean after LT was 22.4 ± 15.9 d (Table 1).

Methods

We collected our data from the unit of LT of our Institute after obtaining written informed consents for operations and researches from recipients and their donors. Our donor's age was > 19 years, furthermore, they underwent the followings: Liver function tests, abdominal ultrasound, liver biopsy, CT angiography, CT volumetric study and psychological assessment. We studied the following.

Preoperative data: Age of donors and recipients, their gender, donors body mass index and liver biopsy, recipient Child Pugh, MELD scores and PHTN. For pre-operative prevention of SFSS; the following strategies were done: (1) appropriate donor selection: (2) steatosis < 10%; (3) donor diet program and/or daily exercise for controlling steatosis in donors; (4) younger donors; (5) in the early cases, estimated (by volumetric study) GRWR < 0.8 were refused, and then in late cases we refused estimated GRWR < 1 for obtaining actual GRWR < 0.8; and (6) appropriate recipient selection by refusing MELD scores < 30.

Intra-operative data: RL or LL grafts, graft with or without MHV, No of HV anastomoses, HV drainage of the RT anterior and/or posterior liver sectors, actual graft weight, and GRWR, performing splenectomy or not, cold ischemia and worm ischemia times per

Table 1 Characteristics of patients and their donors

Character	*n* (%) 174 (100%) (mean ± SD)
Donor age (yr) (mean ± SD)	27.2 ± 6.7
Recipient age (yr) (mean ± SD)	46.5 ± 8.1
Donor gender	
Males	118 (67.8)
Females	56 (32.2)
Recipient gender	
Males	154 (88.5)
Females	20 (11.5)
Child class	
A	9 (5.2)
B	53 (30.5)
C	112 (64.4)
MELD score	
< 18	114 (65.5)
18-24	50 (28.7)
> 24	10 (5.7)
MELD score (mean ± SD)	16.09 ± 4.3
Pre LT PHTN	144 (82.8)
Steatosis	9 (5.2)
Graft type	
Right lobe	166 (95.4)
Left lobe	8 (4.6)
MHV with the graft	
RL graft	10 (5.7)
LL graft	7 (4.1)
No of HV anastomoses	
1	110 (63.2)
2	53 (30.5)
3	10 (5.7)
4	1 (0.6)
Drainage of RT anterior and/or posterior sectors by MHV, V5, V8, and/or RIV in RT lobe grafts (*n* = 166)	56/166 (33.7)
Actual graft weight (g) (mean ± SD)	820.9 ± 174.2
Actual GRWR	1.04 ± 0.2
SFSG (GRWR < 0.8)	17 (9.8)
Splenectomy in SFSG (*n* = 17)	7/17 (41.2)
Cold ischemia time (min) (mean ± SD)	74.9 ± 51.2
Warm ischemia time (min) (mean ± SD)	52.9 ± 15.2
Intraoperative blood transfusion (units) (mean ± SD)	7.05 ± 7.4
Intraoperative plasma transfusion (units) (mean ± SD)	8.2 ± 8.9
Operative time (h) (mean ± SD)	13.1 ± 3.2
Hospital stay post LT (d) (mean ± SD)	22.4 ± 15.9

MELD: Model for end stage liver disease; PHTN: Portal hypertension; MHV: Middle hepatic vein; RIV: RT inferior vein; GRWR: Graft recipient weight ratio; SFSG: Small for size graft.

minutes, plasma and blood transfusion per units and operative time per hours.

For intra-operative prevention of SFSS, the following strategies were done: (1) in the donor operation, with RL graft without middle hepatic vein (MHV) (our standard technique), any short hepatic vein (specially RIV, V5, V8) > 0.5 cm was preserved for possible anastomosis with recipient veins, while MHV was taken with the graft in some cases (dominant MHV and/or SFSG), on the other hand, MHV was taken with all LL grafts except one of them[42]; (2) during back table preparation, the required interposition vein grafts (patch, pantaloon or jumping grafts) that were obtained mainly from the native PV or PUV were reconstructed with the graft veins and prepared for reconstruction with the recipient veins to maximize the liver graft outflow; (3) in the recipient operation, IVC was preserved during explantation of the native liver, the RL graft HV drainage pathways consisted of the RHV without MHV or with it in some cases, furthermore, the RIV, V5 and/or V8 veins were reconstructed in some cases when indicated (Figures 1-4). The standard technique used in reconstruction of the RHV was an end-to side anastomosis between RHV of the graft and the RHV of the recipient with caudal extension to the IVC[43]. However, the LL graft HV drainage pathways consisted of the MHV with the LHV in one stump or separately (N.B the standard technique of HV reconstruction was performing a wide end-to-side anastomosis, between the graft and recipient veins avoiding rotation with extended incision to the vena cava)[3]. It was fundamental to perform complete reconstruction of these pathways of HV outflow to avoid HV congestion of the RL or LL grafts.

The portal vein (PV) reconstruction was then performed in an end-to-end fashion using 3 loupe magnification and by using 6/0 prolene continuous stitches with the routine use of about 1 cm growth factor during tying[44]. After PV reconstruction, doppler ultrasonography (US) was done to assess PV flow (PVF).

Postoperative management: (1) based on our institutional policy and similar to other schools like Japanese school; immunosuppression protocol was as follow: Triple-drug regimen that included calcineurin Inhibitors (CNIs) as FK-506 or cyclosporin, mycophenolate mofetil (MMF), and steroids. Three months after LT, steroids were withdrawn while we performed withdrawal of MMF 6 mo after operation. In late cases, for minimizing the dose of CNI, we administered an interleukin-2 receptor blocker on the day of LT and on the 4th day postoperative; (2) Doppler ultrasonography (PV and HV patency, flow and velocities) was performed routinely just after vascular reconstruction and after closure of the abdomen and then twice daily until the 7th day after operation (POD7), and once per day until hospital discharge; (3) Diagnosis of SFSS: The patients laboratory and clinical parameters (*i.e.*, Serum bilirubin, INR, volume of ascites, and encephalopathy) were followed up to detect the occurrence of SFSS that was classified into small for size dysfunction (SFSD) and small for size non function (SFSNF) (N.B, SFSD is dysfunction of the graft (the presence of persistent hyperbilirubinemia, ascites and coagulopathy) during the early post LT period with absence of other possible causes like Immunological (*e.g.*, graft rejection), technical (*e.g.*, HA or PV obstruction, HV outflow occlusion or biliary leak), infection (*e.g.*, cholangitis). However, SFSS is SFSD or failure of the graft (SFSNF) (loss of graft function leading to patient loss or necessity of retransplantation) during the early post LT period with

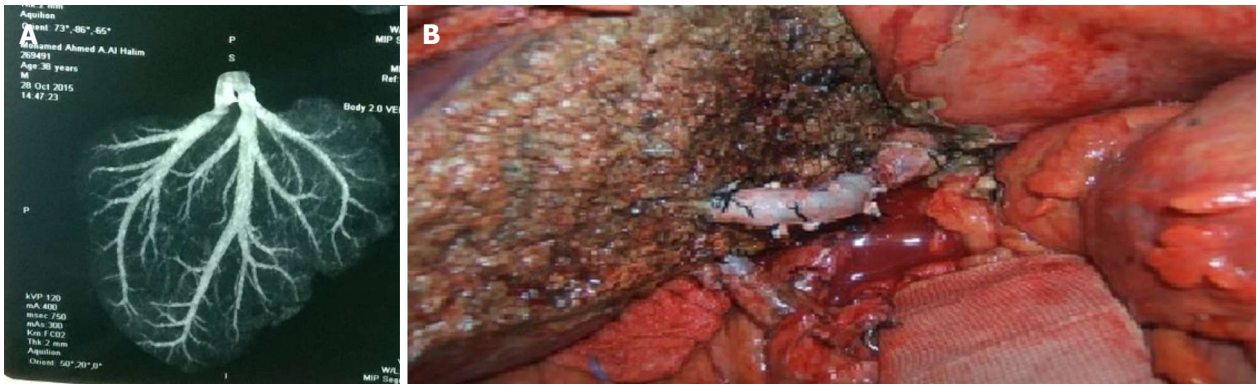

Figure 1 Graft with V5 to be anastomosed with recipient liver transplantation hepatic vein. A: Computed tomography venography showing large V5; B: A jumping graft between the V5 vein of liver graft and liver transplantation hepatic vein of recipient.

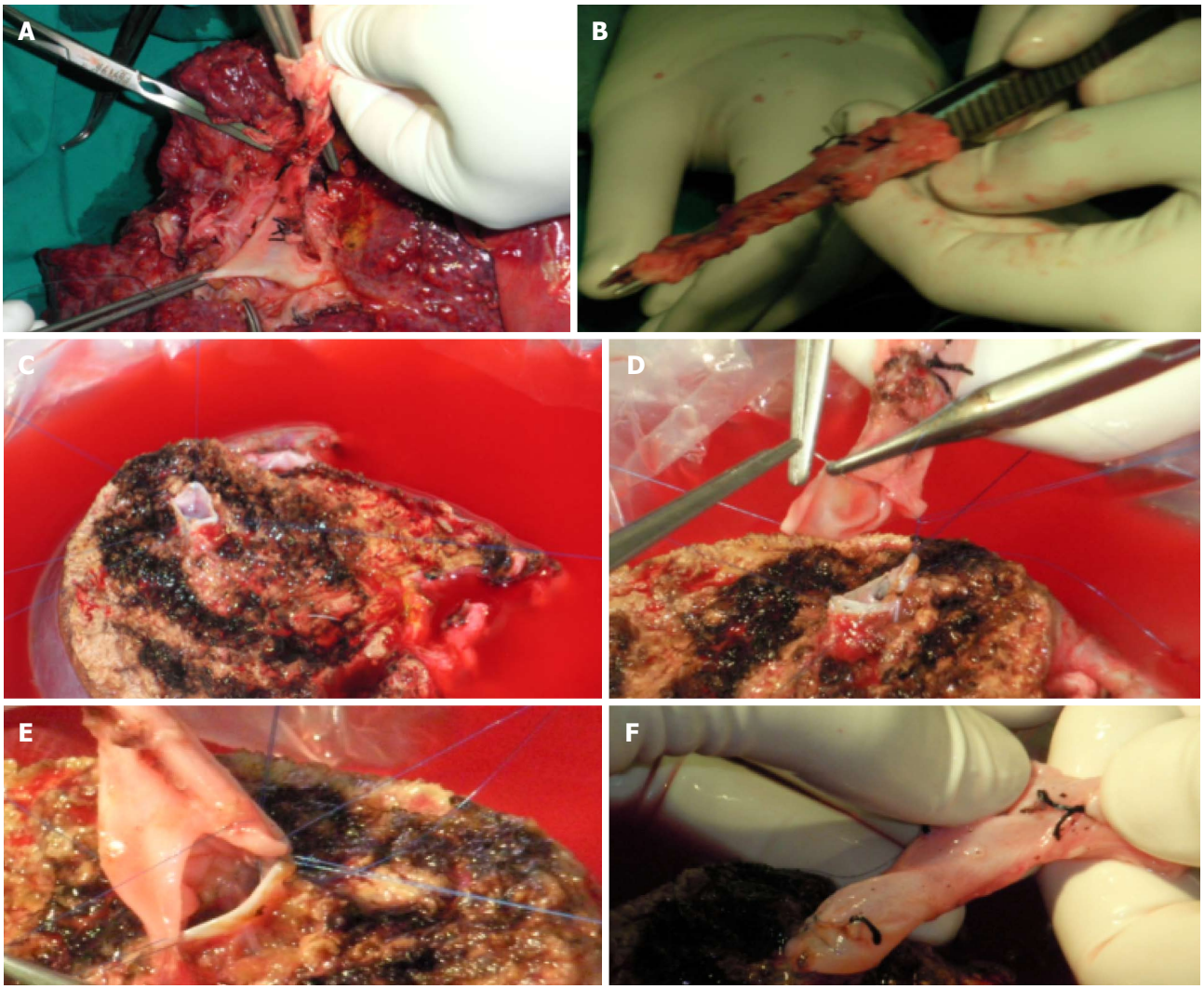

Figure 2 Graft with V8 to be anastomosed with recipient inferior vena cava by jumping graft. A: Obtaining the venous graft from native PV; B: The venous graft; C: V8 vein during back table preparation; D and E: Anastomosing the venous graft to V8; F: Preparation for anastomosing the venous graft to IVC. IVC: Inferior vena cava.

absence of those previously mentioned causes[11]; and (4) management of SFSS: Strategies for prevention were mentioned in the pre- and intra-operative data; furthermore, meticulous post-transplant care was taken in cases with SFSG; Treatment: Right now, very little literature payed attention on how to manage the SFSS after its development; however, oral propranolol (2 × 40 mg/d) and a somatostatin infusion (250-μg

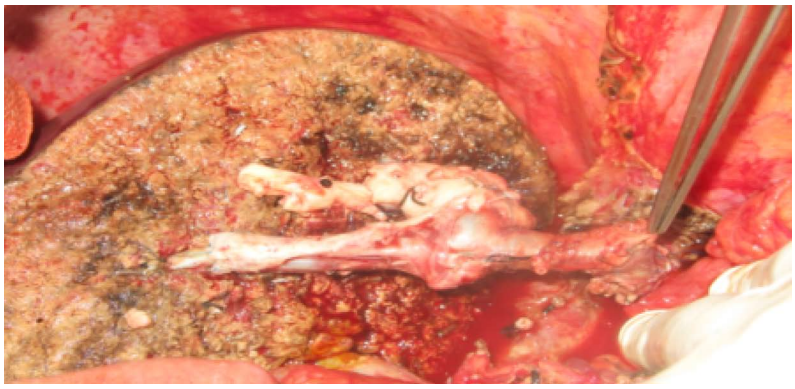

Figure 3 Venous graft obtained from native PUV, portal venous and hepatic vein to communicate 2 V5, 1V8 and right hepatic vein of liver graft with recipient inferior vena cava.

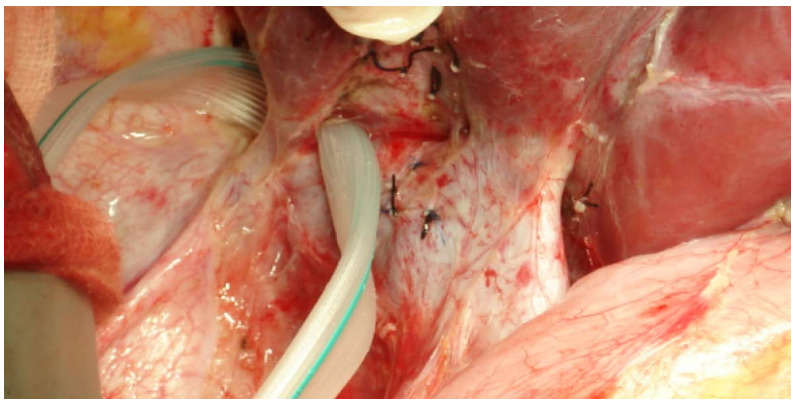

Figure 4 Small right hepatic vein (encircled) and large right inferior vein harvested and anastomosed with recipient inferior vena cava.

bolus followed by perfusion at a rate of 250-50 μg/h for 5 d were given to some of our patients with SFSS to decrease PVF[23,41,45]. Moreover, liver symptomatic support was taken by all patients with the syndrome[15].

Follow-up and outcome of patients: They were followed-up daily until hospital discharge, then weekly until the end of the 1st month then monthly until the end of the follow-up period to detect SFSS and its outcome regarding survival, mortalities, causes of deaths as well as the outcome of SFSG.

Statistical techniques

We used SPSS software (version 21, Chicago, IL, United States) for data processing. Categorical variables were analyzed with the χ^2 or Fisher exact tests. Continuous variables were compared using the student T or Mann whitney tests. The pre-operative, intra-operative and post-operative variables were descriptively studied. We did comparison between patients with and without SFSS regarding the pre- and intra-operative variables using univariate analysis and then multivariate analysis. Furthermore, their outcome as well as cause of death was compared by univariate analyses. On the other hand, Kaplan-Meier curve was applied and plotted for survival analysis (patient and graft survival) and the log-rank tests were used for comparing patient and graft survival according to SFSS and for comparing patient survival according to SFSG. In the previous tests, if *P* value was < 0.05, it was considered significant.

RESULTS

Some characteristics of patients with SFSS

SFSS was diagnosed in 20 (11.5%) of our recipients where, SFSD affected 16 of patients (80%) and SFSNF was present in four patients (20%). Persistent hyperbillirubinaemia, ascitis, and coagulopathy affected 100%, 90%, and 85% of our SFSS cases respectively, where; all the 16 patients with SFSD had persistent hyperbilirubinemia, ascites and coagulopathy during the early post-LT period; however, all the 4 cases with SFSNF had persistent hyperbilirubinaemia, 2 of them had massive ascites and one of them had coagulopsthy; furthermore, they developed graft failure and died from SFSS complications (*e.g.*, Sepsis, MOF, ARDS, DIC) during the 1st week post-transplant. Regarding graft size in patients with SFSS, 10, 5, and 5 of patients had extra-small graft (SFSG, GRWR < 0.8), small graft (GRWR ⩾ 0.8 and < 1) and medium sized graft (GRWR ⩾ 1) respectively. Extra small

Table 2 Some characteristics of patients with small for size syndrome

Character	*n* (%)
SFSS	20 (100)
Type of SFSS	
SFSD	16 (80)
SFSNF	4 (20)
Main presentation	
Hyperbilirubinaemia	20 (100)
Large volume of ascites	18 (90)
Coagulopathy	17 (85)
Graft size	
GRWR < 0.8 (SFSG)	10 (50)
GRWR ⩾ 0.8 and < 1	5 (25)
GRWR ⩾ 1	5 (25)
Main aetiology of SFSS	
Extra small graft (SFSG)	10 (50)
Portal hyperperfusion	3 (15)
Severe PHTN	4 (20)
Outflow obstruction	3 (15)

SFSS: Small for size syndrome; SFSD: Small for size dysfunction; SFSNF: Small for size non function; PHTN: Portal hypertension.

graft (SFSG), portal hyperperfusion, severe PHTN, and venous outflow obstruction were the main direct causes of SFSS in 10 (50%), 3 (15%), 4 (20%), and 3 (15%) of patients respectively. Moreover; Portal hyperperfusion was assessed by doppler US post operatively, severe PHTN was the persistent pre transplant severe PHTN that was assessed by complete history, clinical examination laboratory and imaging, lastly, venous outflow obstruction was known by post-transplant doppler ultrasonography US (Table 2).

Comparison between patients with and without SFSS

The following variables were statistically significant predictors of SFSS on univariate analysis, Pre LT PHTN, graft steatosis, LL graft, SFSG, mean actual graft weight 640.50 ± 211.049 g, mean actual GRWR 0.862 ± 0.2158 g and mean intra-operative plasma transfusion 11.40 ± 7.816 units. On the other hand, there was lower incidence of SFSS in patients with SFSG who underwent splenectomy [4/10 (40%) SFSS *vs* 3/7 (42.9%) no SFSS] but without statistical significance, However, there was none significant lower incidence of the syndrome in patients with RL graft when drainage of the RT anterior and/or posterior sectors by MHV, V5, V8, and/or RIV was done [4/10 (28.6%) SFSS *vs* 52/152 (34.2%) no SFSS], furthermore, there was lower incidence of the syndrome in patients with RL graft without MHV who underwent reconstruction of V5, V8 and/or RIV [3/13 (23.1%) SFSS *vs* 43/143 (30.1%) no SFSS] but without statistical significance. On the other hand, Child score, MELD score, cold and worm ischemia times had no effect on occurrence of the syndrome (Table 3).

On multivariate analysis, mean actual graft weight 640.50 ± 211.049 g, and mean actual GRWR 0.862

Table 3 Comparison between patients with and without small for size syndrome (Univariate analysis)

Character	SFSS, *n* (%) 20 (100) (mean ± SD)	No SFSS, *n* (%) 154 (100) (mean ± SD)	*P* value
Child class			< 0.05
A	1 (5)	8 (5.2)	
B	7 (35)	46 (29.9)	
C	12 (60)	100 (64.9)	
MELD score			< 0.05
< 18	16 (80)	98 (63.6)	
18-24	4 (20)	46 (29.9)	
> 24	0 (0)	10 (6.5)	
Pre LT PHTN			0.046
Yes	20 (100%)	128 (83.1%)	
No	0 (0)	26 (16.9%)	
Steatosis			0.035
Yes	3 (15)	6 (3.9)	
No	17 (85)	148 (96.1)	
Graft type			0
RL	14 (70)	152 (98.7)	
LL	6 (30)	2 (1.3)	
SFSG (GRWR < 0.8)			0
Yes	10 (50)	7 (4.5)	
No	10 (50)	147 (95.5)	
Actual graft weight (g) (mean ± SD)	640.50 ± 211.049	844.39 ± 154.888	0
Actual GRWR (g) (mean ± SD)	0.862 ± 0.2158	1.065 ± 0.1922	0.001
Cold ischemia time (min) (mean ± SD)	73.95 ± 55.350	75.13 ± 50.923	< 0.05
Warm ischemia time (min) (mean ± SD)	50.95 ± 14.248	52.08 ± 16.336	< 0.05
Intraoperative plasma transfusion (units) (mean ± SD)	11.40 ± 7.816	7.81 ± 8.943	0.021
No. of HV anastomoses			< 0.05
1	11 (55)	99 (64.3)	
2	8 (40)	45 (29.2)	
3	1 (5)	9 (5.8)	
4	0 (0)	1 (0.6)	
Splenectomy in patients with SFSG (*n* = 17)			< 0.05
Yes	4 (40)	3 (42.9)	
No	6 (60)	4 (57.1)	
Drainage of RT anterior and/or posterior sectors (MHV, V5, V8, RIV) in RL graft with or without MHV (*n* = 166)			< 0.05
Yes	4 (28.6)	52 (34.2)	
No	10 (71.4)	100 (65.8)	
MHV reconstruction in patients with RL graft (*n* = 166)			< 0.05
Yes	1 (7.1)	9 (5.9)	
No	13 (92.9)	143 (94.1)	
Drainage of RT anterior and/or posterior sectors (V5, V8, RIV) in RL graft without MHV(*n* = 156)			< 0.05
Yes	3 (23.1)	43 (30.1)	
No	10 (76.9)	100 (69.9)	

MELD: Model for end stage liver disease; Pre LT PHTN: Pre liver transplant portal hypertension; RL: Right lobe; LL: Left lobe; SFSG: Small for size graft; GRWR: Graft recipient weight ratio; MHV: Middle hepatic vein; RIV: Right inferior vein.

Table 4 Multivariate analysis of predictors of small for size syndrome (Binary logistic regression)

	P value	Exp(B)	95%CI for EXP (B)	
			Upper	Lower
Pre LT PHTN	0.998	0.00	0.000	
Steatosis	0.060	0.145	0.020	1.074
Graft type	0.166	6.407	0.463	88.717
Actual GRWR < 0.8	0.050	4.303	1.024	18.082
Actual graft WT	0.030	1.004	1.000	1.008
Intraoperative plasma transfusion (units)	0.235	0.963	0.905	1.025

Pre LT PHTN: Pre liver transplant portal hypertension; GRWR: Graft recipient weight ratio.

± 0.2158 g were the only independent predictors of SFSS, however, graft steatosis had trend towards independence (*P* = 0.06) (Table 4).

Outcome of patients

Patients with SFSG had statistically significant higher mortality than those without SFSG (76.5% *vs* 40.8%, *P* = 0.005), furthermore, mortality was significantly higher in SFSS patients than those without SFSS (75% *vs* 40.3%, *P* = 0.003), On the other hand, the most frequent cause of death in patients with the syndrome was the syndrome itself and its complications (*i.e.*, Sepsis, graft failure, DIC, renal failure, ARDS, and MOF), furthermore, the 4 cases with SFSNF died during the 1st week post LT due to the syndrome complications (*e.g.*, sepsis, MOF, ARDS, DIC) and the other 16 cases with SFSD were classified into: Five a live patients, 2 patients died from post LT bleeding, and 9 patients died from the syndrome complications (*i.e.*, Sepsis, graft failure, DIC, renal failure, ARDS, MOF). However, sepsis was the most frequent reason for mortality in non SFSS patients 19 (30.6%); moreover, MOF from causes other than SFSS, post-operative bleeding, intra-operative bleeding, PVT, renal impairment from causes other than SFSS, metastatic cholangiocarcinoma, early graft dysfunction from causes other than SFSS, HCC recurrence, ischemic reperfusion injury, HAT were the other causes of death in 11 (17.7%), 10 (16.1%), 8 (12.9%), 4 (6.4%), 2 (3.2%), 2 (3.2%), 2 (3.2%), 2 (3.2%), 1 (1.6%), and 1 (1.6%) of them respectively. Regarding clavien grading, all the previous causes of death in both groups were grade V. The 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients with SFSS were 30%, 30%, 25%, 25%, 25% and 25% respectively, while, the 6-mo, 1-, 3-, 5-, 7- and 10-year survival in patients without SFSS were 70.1%, 65.6%, 61.7%, 61%, 59.7%, and 59.7% respectively, with statistical significant difference. Lastly, graft survival in patients with SFSS was 20%, however it was 57.8% in patients without the syndrome with statistical significant difference (*P* = 0.001) (Table 5 and Figure 5).

DISCUSSION

SFSS limits LT expansion; furthermore, it is the major cause of worse short-term prognosis after LDLT[17]. Therefore, better understanding of its pathogenesis, risk factors, strategies for prevention and treatment may improve outcomes after LDLT.

The incidence of SFSS in LL LDLT is higher than RL LDLT (20% *vs* 10%)[46]; as the LL graft gives only about 40 % of the needed liver mass that affect the metabolic demands of adult recipients leading to SFSS[1,18,47]. Similarly, the syndrome rate was significantly higher in our LL LDLT than RL LDLT (75% *vs* 8.4%, *P* = 0.000), and this was due to small NO of our LL LDLT (eight cases), where six of them (75%) had SFSG. On the other hand, LL SFSG was the only independent predictor of graft dysfunction in Yi *et al*[48] (2008) study. However, SFSS rate was 22.2%, and 19.5% in LL LDLT of Soejima *et al*[7] (2003), and Soejima *et al*[49] (2012) studies respectively, and 11.5% in our study that included mainly RL LDLT(166 cases). On the other hand, it was 9.6% and 12.5% in LDLT of Gruttadauria *et al*[50] (2015) and Ben-Haim *et al*[32] (2001) studies respectively. In contrast, it was higher (22.7%, 50% and 37.5%) in RL LDLT of Goralczyk *et al*[15] (2011), LL LDLT of Katsuragawa *et al*[51] (2009) and LL LDLT of Lauro *et al*[52] (2007) studies respectively, and obviously lower (6.3%) in Botha *et al*[53] (2010) study.

SFSS is a disease related to partial liver grafts denoting its inability to perform the functional requirements of the adult recipients resulting in hepatic dysfunction and/or failure and usually manifests as hyperbilirubinemia, ascites, coagulopathy, and encephalopathy[15,19,23,40,46,47]. Furthermore, it is characterized microscopically by cholestasis, hemorrhagic necrosis around the central veins and ballooning of hepatocytes due to microcirculatory disturbances[54]. Similarly, the syndrome was presented by hyperbilirubinemia, ascites, and coagulopathy in 100%, 90%, and 85% of our patients respectively. Moreover, we had 4 (20%) cases with SFSNF and 16 (80%) patients with SFSD.

The principal pathogenesis of SFSS is the unbalance between regeneration of the liver and the increased liver function demand, resulting in graft dysfunction[1]. Furthermore, it is clear that the syndrome is not just caused by SFSG, but also by multiple factors including technical issues, quality of the graft, and recipient factors[3,18,22,32,55,56] (where, the balance between PV inflow, outflow of HV, and functional mass of liver determines its development)[17]. So, for preventing SFSS, it is important to increase the graft volume, and to control adequate PV inflow and HV outflow by the surgical and the none surgical techniques[34]. On the other hand we divided our strategies for preventing the occurrence of the syndrome into pre-operative and intra-operative ones.

The required graft size for successful LT is 30%-40% of the expected liver volume for the recipient (GV/SLV) or 0.8%-1.0% of the body weight (GRWR)[19]; as the insufficient graft size is the primary cause of SFSS due to the relative shortage of hepatic parenchymal cells[2,3,12,16,17,55]; furthermore, SFSG suffers from a

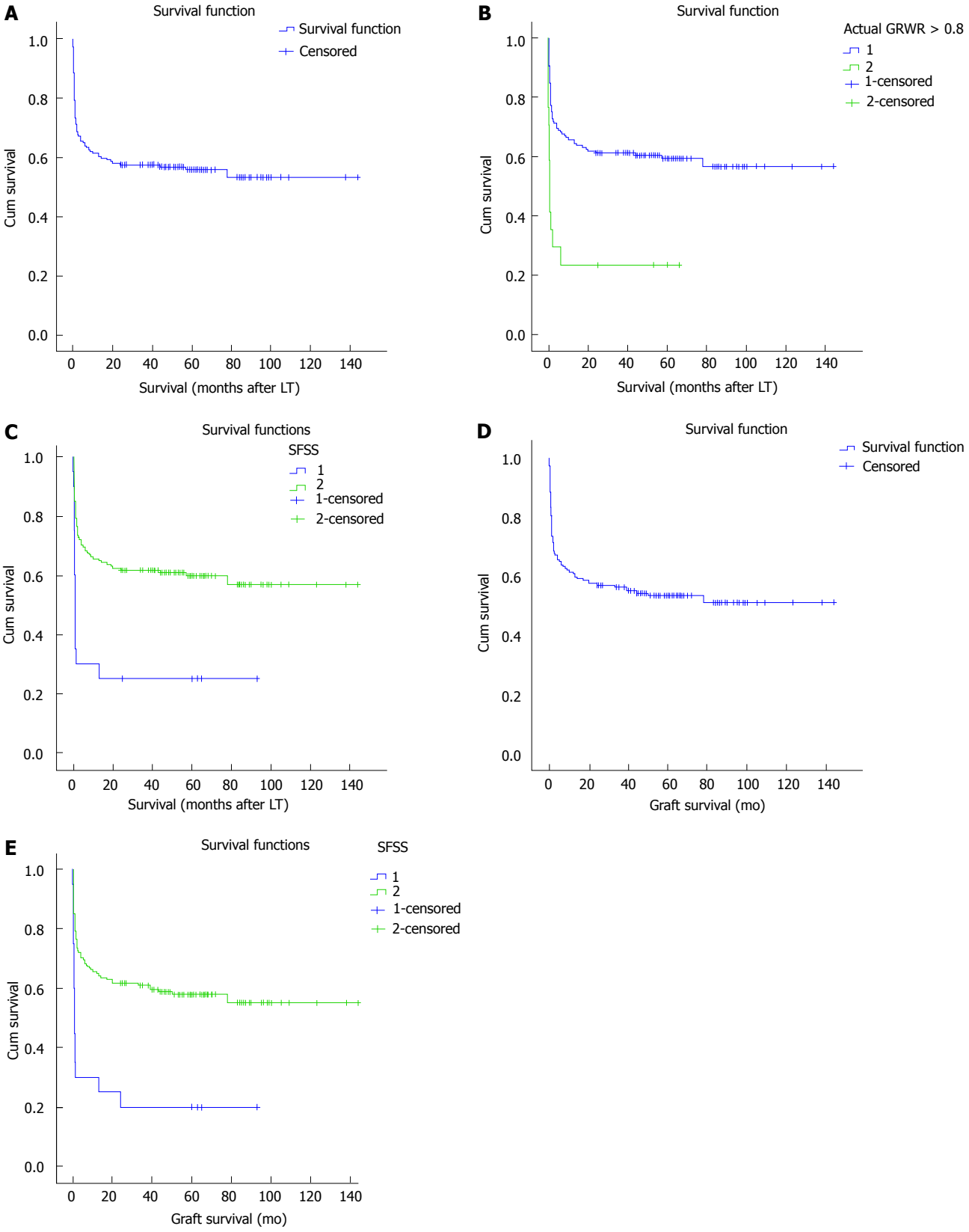

Figure 5 Kaplan-Meier survival curves (1, 2, 3). A: KM survival curve; B: SFSG and survival [SFSG (GRWR < 0.8) = 2, Log-Rank = 0.00]; C: SFSS and survival (SFSS = 1, Log-Rank = 0.00); D: KM graft survival curve; E: SFSS and graft survival (SFSS = 1, Log-Rank = 0.00). SFSG: Small for size graft; GRWR: Graft recipient weight ratio; SFSS: Small for size syndrome.

transient PHTN early after reperfusion, that is associated with up-regulation of endothelin-1 in the graft and ultra-structural evidence of sinusoidal damage[8], so, the incidence of SFSS increases when the graft

Table 5 Outcome of patients

Total number	SFSS *n* (%) 20 (100)	-	No SFSS *n* (%) 154 (100)	-	*P* value
Overall mortality	15 (75)	Grade	62 (40.3)	Grade	0.003
Cause of mortality and their Dindo-Clavien score					
Sepsis from causes other than SFSS	0	-	19 (30.6)	V	0
SFSS (sepsis, graft failure, DIC, renal failure, ARDS, MOF)	13 (86.7)	V	0	-	
MOF from causes other than SFSS	0	-	11 (17.7)	V	
Post-operative bleeding	2 (13.3)	V	10 (16.1)	V	
Intra-operative bleeding	0	-	8 (12.9)	V	
PVT	0	-	4 (6.4)	V	
Renal impairment from causes other than SFSS	0	-	2 (3.2)	V	
Metastatic cholangiocarcinoma	0	-	2 (3.2)	V	
Early graft dysfunction from causes other than SFSS	0	-	2 (3.2)	V	
HCC recurrence	0	-	2 (3.2)	V	
Ischemic reperfusion injury	0	-	1 (1.6)	V	
HAT	0	-	1 (1.6)	V	
6-mo survival	6 (30)	-	108 (70.1)	-	0.000
1-yr survival	6 (30)	-	101 (65.6)	-	0.002
3-yr survival	5 (25)	-	95 (61.7)	-	0.002
5-yr survival	5 (25)	-	94 (61)	-	0.002
7-yr survival	5 (25)	-	92 (59.7)	-	0.003
10-yr survival	5 (25)	-	92 (59.7)	-	0.003
Survival per months (mean ± SD)	16.3 ± 28.9	-	39.9 ± 34.3	-	0.002
Graft survival	4 (20)		89 (57.8)		0.001
Graft survival per months (mean ± SD)	16.2 ± 28.9		39.7 ± 34.3		0.003

SFSS: Small for size syndrome; DIC: Disseminated intravascular coagulation; ARDS: Adult respiratory distress syndrome; MOF: Multi organ failure; PVT: Portal vein thrombosis; HCC: Hepatocellular carcinoma; HAT: Hepatic artery thrombosis.

is SFSG[11,23,52,57]. In Similar, SFSG was independent predictor of SFSS in Lei *et al*[58] (2012) study, similarly, SFSG was the most frequent cause of SFSS (50%) in our series, and the only independent predictor of it in our multivariate analysis despite our efforts to decrease SFSG by selecting larger-sized RL graft and by selecting donors with estimated GRWR > 1(in our late cases) as a pre-operative strategy for preventing SFSS. In contrast, Graft size had no impact on SFSS in Shimazu *et al*[59] (2004), and Ikegami *et al*[60] (2009) studies.

Although, SFSS is frequently encountered in SFSG (GRWR < 0.8), it may also be found in recipients of larger grafts (GRW > 0.8)[9,10,61-64]. Similarly, in our work the incidence of SFSS in normal size graft (GRWR > 0.8) was 6.4% (10/157); and this was due to the effect of other negative factors.

Steatotic liver grafts should not be used if the graft volume is small to avoid SFSS[16,17]; furthermore, graft steatosis is an exclusion criterion for donation in LDLT[65]. The mechanisms of poor steatotic graft function after reperfusion include defective anaerobic metabolism of the fatty hepatocytes, decreased lumen of sinusoids by the fat droplets, and higher free radicals caused by lipid peroxidation[3,27]. In similar, severe steatosis was significantly associated with poor function post LDLT in Hayashi *et al*[66] (1999) study. In addition, despite our refusal of grafts with steatosis > 10% to avoid the occurrence of SFSS, steatosis was significant predictor of SFSS in our univariate analysis; moreover it had a trend towards being independent predictor in multivariate analysis. In contrast, graft steatosis had no impact on graft dysfunction in Yi *et al*[48] (2008) study. Similarly, Sterneck *et al*[67] (1995) reported that grafts with mild to moderate steatosis had good function, and Soejima *et al*[56] (2003) found that a graft with 20%-50% macrovesicular steatosis (moderate grade) was accepted for transplantation.

Because LDLT is a scheduled procedure, daily exercise and diet control are required for steatosis control in donors[1,4]. In similar, donor diet programs and/or daily exercise for controlling steatosis in our donors were parts of our preoperative strategies for avoiding SFSS.

The principal mechanism in SFSS seems to be sinusoidal shear stress secondary to increased PV pressure (PVP) and/or PVF which cause graft over-perfusion leading to hepatic microcirculatory disturbance, hepatocyte functional insufficiency, over-regeneration of the hepatocytes, hepatocellular damage and death[3,16,17,19,20,23,46,51,52,68]; furthermore, Portal hyper-perfusion and insufficient venous outflow decrease the arterial perfusion (the so-called hepatic arterial buffer response), with a reduced capacity for regeneration, resulting in impaired liver function[18,19,23,69]; Similarly, portal inflow volume was independent predictor of SFSS in Lei *et al*[58] (2012) study. In similar, in our work, pre LT PHTN was significant predictor of SFSS in univariate analysis; furthermore, severe pre LT PHTN that persisted post LT was the etiology of the syndrome in 4 (20%) of our cases of SFSS, however, portal hyper-perfusion (identified by doppler US) was the cause of it in 3 (15%) of them.

One of the ways to get portal decompression is depriving the splenic part of portal flow by splenectomy[3,17,19,39,46,51,52,68,70]. Furthermore, splenectomy increases the HA blood flow leading to increased oxygen supply[18]. Similarly, we did splenectomy in 7/17 of our patients with SFSG to decrease portal overflow that lead to non-significant lower incidence of the syndrome (40% SFSS *vs* 42.9% no SFSS).

Theoretically, a RL graft including MHV is the best graft for LDLT regarding the recipients; but, this type of graft is not performed in most major transplant centers due to increased donor risk by decreasing the residual volume of the liver[3,23]. So, the RL graft without MHV is the standard technique in A-ALDLT[1,15,71]; however deprivation of the anterior segment venous drainage cause graft congestion, leading to graft dysfunction in spite of the increased volume of the graft[1,25,26,36]. Therefore, reconstruction of the anterior segments drainage veins (V5/V8)[15,17,23,72,73] with or without the reconstruction of the RIV is frequently necessary to prevent this[3]. Similarly, in our series, RL graft without MHV was our standard technique of LT, moreover, we did reconstruction of V5, V8 and/or RIV in 46/156 of our patients with RL graft without MHV that lead to non-significant lower rate of the syndrome (23.1% SFSS *vs* 30.1% no SFSS). Nevertheless, venous outflow obstruction (Known by doppler US) was the reason for the syndrome in 3 (15%) of our SFSS cases. In addition, venous outflow capacity was independent predictor of SFSS in Lei *et al*[58] (2012) study.

Early graft function is better when the graft is given by a younger donor[74,75]; as, the grafts from older donors have diminished regenerative capacity[75,76], lower blood flow and poor function due to aging[18]. Similarly, Ikegami *et al*[77] (2000) in their LL LDLT, found that regeneration of grafts from older donors of LDLT were inferior to those of grafts from younger ones and Tanemura *et al*[78] (2012), in their RL LDLT reported that donor age equal or more than 50 years was independent predictor of impaired regeneration of remnant liver at 6 mo post LT, furthermore, donor age was significant predictor of graft dysfunction and poor graft survival in Yi *et al*[48] (2008) and Moon *et al*[79] (2010) studies, and was independent predictor of SFSS in Sanefuji *et al*[80] (2010) study, while Ikegami *et al*[29] (2008) found that grafts from younger donors had lower bilirubin levels and ascites production post LDLT. On the other hand, in their RL LDLT, the Kyoto group reported that the functional recovery of recipients from older donors was comparable to that of those from younger ones[81]. Similarly, donor age was not significant predictor of SFSS in our series where our donors had younger age (mean = 27.2 ± 6.7 years).

Both warm[30] and cold ischemia times[31] impair regeneration after LDLT. Conversely, in our series, there was no significant correlation between cold or worm ischemia times and SFSS occurrence. Similarly, ischemia time did not affect graft function in Yi *et al*[48] (2008) study.

A higher MELD score has negative insult on graft function that may cause its dysfunction or failure especially in SFSG; due to its inability to meet the increased metabolic and synthetic demands of those high-risk recipients with severely damaged liver function[1,16,17]. In similar, MELD score was independent predictive of SFSS in Lei *et al*[58] (2012) study. However, Yoshizumi *et al*[75] (2008) reported that a larger liver graft is necessary with older donors (> 50 years) and higher MELD score (> 20), and Emiroglu *et al*[82] (2007) mentioned that recipients with high MELD scores should be given grafts only when their GRWR is > 1 to improve graft survival also, Ikegami *et al*[77] (2000) recommended that patients with high-risk should be given a younger and larger grafts to minimize the risk of SFSS. On the other hand, pre-operative MELD score did not affect SFSS rate in our work.

The preoperative Child Pugh score is mostly associated the portal hyper-perfusion state after LT leading to SFSS[1,18]. Similarly, Ben-Haim *et al*[32] (2001) reported that patients with severe decompensation (Child B, C) require larger grafts to prevent occurrence of SFSS, while, Soejima *et al*[7] (2003) found that the rate of SFSS after A-A LDLT was higher in cirrhotic patients (43.8%) in comparison with non-cirrhotics (5%). Conversely, there was no significant correlation between Child score and SFSS in our work.

Most literature mentions how to prevent SFSS occurrence. However, very few literatures discuss the treatment of this syndrome after its occurrence. In Goralczyk *et al*[15] (2011) study, most SFSS cases were treated with successful symptomatic therapy. Furthermore, intravenous octreotide, and oral propranolol were found to decrease the hyperbilirubinemia and coagulopathy seen in patients with SFSS in Ozden *et al*[41] (2007) study. On the other hand, symptomatic liver support was given to all our patients with SFSS but with poor outcome; moreover, oral propranolol and a somatostatin infusion were given to some of our patients with SFSS to decrease portal flow and improve the syndrome outcome but also with poor outcome.

Approximately 50% of recipients with SFSG die of sepsis 4 to 6 wk after LT[83]; moreover survival rates of patients with SFSG are worse than those with adequate graft size[2,12]. In similar, SFSG was significant predictor of poor survival in our work (P = 0.005), also, it had negative impact on survival in Lo *et al*[84] (1999), Sugawara *et al*[55] (2001), and Lee *et al*[8] (2004) studies. Furthermore, it was independent predictor of graft loss in Katsuragawa *et al*[51] (2009) study. Conversely, SFSG did not affect survival in Shimazu and Kitajima[59] (2004), Shimada *et al*[85] (2004), Ikegami *et al*[60] (2009), Selzner *et al*[86] (2009), Moon *et al*[79] (2010), Kaido *et al*[47] (2011), and Li and Li[87] (2013) studies.

SFSS results in higher incidence of septic compli-

cations, pulmonary failure, renal failure, and increased mortality[22,23,46], furthermore, it causes prolonged hospitalization, graft and patient loss[15]. Similarly, in our series, SFSS lead to significant higher mortality rate (P = 0.003), and the most frequent cause of death was the syndrome itself and its complications (*i.e.*, sepsis, graft failure…). In similar, recipients who developed SFSS had inferior patient survival in Soejima *et al*[7] (2003), and Lauro *et al*[52] (2007) studies. In addition, it was the direct cause of 3 mortalities in Soejima *et al*[43] (2006) study. In conclusion: SFSG is the independent and main factor for occurrence of SFSS after A-ALDLT leading to poor outcome. However, the management of this catastrophe depends upon its prevention (*i.e.*, selecting graft with proper size, splenectomy to decrease portal venous (PV) inflow, and improving HV outflow by reconstructing large draining veins of the graft).

COMMENTS

Background

Small for size syndrome (SFSS) is dysfunction of the graft (the presence of persistent hyperbilirubinemia, ascites and coagulopathy) during the early post liver transplantation (LT) period with absence of other possible causes like technical, immunological or infection causes, or failure of the graft (loss of its function leading to patient loss or necessity of retransplantation) during the early post LT period with absence of the previously mentioned causes. Small for size graft (SFSG) is the independent and main factor for occurrence of this syndrome that limits LT expansion and leads to worse short-term prognosis after living donor liver transplantation (LDLT). Therefore, better understanding of SFSS pathogenesis, risk factors, strategies for prevention and treatment may improve outcomes after LDLT. Moreover, the management of this catastrophe depends mainly on its prevention by pre-, intra- and post- operative measures like selecting graft with proper size, proper control of portal vein (PV) inflow and hepatic vein (HV) outflow.

Research frontiers

SFSG is the independent and main factor for occurrence of SFSS after A-ALDLT leading to poor outcome; so it is crucial to select graft with proper size to avoid this catastrophic complication. Furthermore, proper control of PV inflow by splenectomy and HV outflow by reconstruction of large tributaries of graft HV may prevent occurrence of this syndrome, however, these conclusions need further studies.

Innovations and breakthroughs

The study goes with other literature studies that mentioned the correlation between SFSG and SFSS and their negative insult on outcome after A-A LDLT, however, the innovation and breakthroughs in the work is that the authors gave an idea about the important rule of intra-operative splenectomy (specially in SFSG) as well as the meticulous reconstruction of HV tributaries of liver graft in preventing the occurrence of this syndrome (despite the non-statistical significance), as the literature data is very few regarding these points.

Applications

The study emphasizes the rule of pre-, intra- and post-operative strategies for prevention of SFSS as selection of graft with proper size. Furthermore, the authors encourage performing further studies to emphasize the rule of intra-operative splenectomy as well as the rule of reconstructing large HV tributaries of the transplanted liver graft in preventing the occurrence of SFSS.

Terminology

SFSG: Is the graft where graft recipient weight ratio (GRWR) < 0.8; SFSD: It is dysfunction of the graft (the presence of persistent hyperbilirubinemia, ascites and coagulopathy) during the early post LT period with absence of other possible causes like Immunological (*e.g.*, graft rejection), technical (*e.g.*, HA or PV obstruction, HV outflow occlusion or biliary leak), infection (*e.g.*, cholangitis); SFSNF: Failure of the graft (loss of its function leading to patient loss or necessity of retransplantation) during the early post LT period with absence of those previously mentioned causes; SFSS: SFSD and/or SFSNF.

Peer-review

It is an interesting quite large series.

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ORIGINAL ARTICLE

Observational Study

Outcomes of pregnancy in patients with known Budd-Chiari syndrome

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Abstract

AIM

To analyse the risk of pregnancy (a prothrombotic state) in patients with Budd-Chiari Syndrome (BCS).

METHODS

Retrospective study of pregnancy in women with known BCS at single center from January 2001 to December 2015.

RESULTS

Out of 53 females with BCS, 7 women had 16 pregnancies. Median age at diagnosis of BCS in these women was 25 years (range 21-34 years). At least one causal factor for BCS was identified in 6 women (86%). Six women had undergone radiological decompressive treatment. All patients had anticoagulation. Six fetuses were lost before 20 wk gestation in 2 women. There were 9 deliveries over 32 wk gestation and one delivery at 27 wk. All infants did well. Seven babies were born by emergency caesarean section. There were no cases of thrombosis. Two patients had notable vaginal (PV) bleeding in 3 pregnancies. None of the patients had variceal haemorrhage. Two patients were diagnosed with pulmonary hypertension, one during pregnancy

and the other in the post-partum period. There was no maternal mortality.

CONCLUSION

Maternal outcomes in patients with treated BCS are favourable and fetal outcomes beyond 20 wk gestation are good. There has been increased rate of caesarean section. Pulmonary hypertension is an important finding that needs further validation. These patients should be managed in centers experienced in treating high-risk pregnancies.

Key words: Budd-Chiari syndrome; Pregnancy; Portal hypertension; Pulmonary hypertension; Thrombophilia

Core tip: Pregnancy is a prothrombotic state and can cause adverse outcome in patients with Budd-Chiari syndrome (BCS). In our study, maternal outcome in patients with known and treated BCS was good. However, most deliveries were carried out by emergency caesarean section (7/10). There was high incidence of placental disease leading to caesarean section. Fetal outcome beyond 20 wk gestation was also good. With careful monitoring of anti-coagulation, there were no cases of thrombosis and only a minority of patients had noteworthy bleeding complications. Development of pulmonary hypertension in two patients several years after TIPSS is an important finding that warrants further studies.

Khan F, Rowe I, Martin B, Knox E, Johnston T, Elliot C, Lester W, Chen F, Olliff S, Mehrzad H, Zia Z, Tripathi D. Outcomes of pregnancy in patients with known Budd-Chiari syndrome. *World J Hepatol* 2017; 9(21): 945-952 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i21/945.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i21.945

INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare disorder caused by hepatic venous outflow obstruction and resulting hepatic dysfunction due to sinusoidal congestion, ischaemic injury to the liver and portal hypertension. The main mechanism for BCS is thrombosis of the hepatic veins or of the terminal portion of the inferior vena cava[1,2]. The management using a stepwise regimen is largely successful with anticoagulation and interventional radiology alone. Stepwise regimen includes; (1) anticoagulant therapy for an indefinite period of time; (2) angioplasty or stenting for stenosis of hepatic veins; and (3) decompressive techniques [surgical shunt or transjugular intrahepatic porto-systemic shunts (TIPSS)], for patients who are non-responsive to medical treatment or not candidates for angioplasty/stenting[3]. TIPSS has a lower morbidity and mortality rate than surgery and is a preferred approach**.** The outcomes are favourable with 10-year survival approaching 90%[4,5].

Usually multiple risk factors for venous thromboembolism are present in patients with BCS[1,6-8]. In one study, 84% of 163 patients with BCS had at least one thrombotic risk factor, and 46% of these patients had more than one prothrombotic risk factor; the most common was myeloproliferative neoplasia (MPN) (49% of 103 tested patients)[9]. In another study of 43 women with BCS, at least one thrombotic risk factor (not considering pregnancy as risk factor) was identified in 40 women (93%) including MPN in 56% of study participants[10]. Other thrombotic risk factors include mutation in Factor V Leiden and prothrombin gene, protein C, protein S or antithrombin deficiency, antiphospholipid syndrome, hyperhomocysteinemia and paroxysmal nocturnal haemoglobinuria. BCS may also be a complication of systemic vasculitides such as Bechet's disease[11].

BCS mainly affects women of childbearing age and pregnancy can be a crucial issue. There is conflicting data on prevalence of pregnancy related BCS. A systematic review and meta-analysis of twenty studies demonstrated a pooled prevalence of pregnancy-related BCS of 6.8%[12]. However another study showed that pregnancy is unlikely to cause BCS in the absence of other thrombotic risk factors[10].

Pregnancy is a hypercoagulable state and earlier studies reported that women with BCS could be at risk of developing severe exacerbation of their underlying disease during pregnancy[13,14]. Rautou *et al*[15] conducted a study on outcome of pregnancy in women with known and treated BCS and concluded that good maternal outcome could be achieved with current treatment modalities and close surveillance of BCS. Therefore, BCS cannot be considered a contraindication to pregnancy in stable patients with well-controlled disease.

As the available literature on pregnancy complications in women with known BCS remains scarce, we performed this study of women treated at our tertiary centre for BCS who had become pregnant.

MATERIALS AND METHODS

We used the definitions related to outcome of pregnancies as previously described by Rautou *et al*[15]: (1) date of diagnosis of BCS: the first imaging modality showing an obstructed venous outflow tract; and (2) miscarriages: A spontaneous loss of pregnancy before 20 weeks' of gestation. Outcome of the pregnancy: (1) favourable: Live birth occurred at 32 or more completed weeks of gestation, with a healthy infant and no serious obstetrical complication (bar intrahepatic cholestasis); and (2) poor: Otherwise pregnancy outcome. Rotterdam prognostic index was calculated as previously described[16].

The electronic records of all female patients dia-

gnosed with BCS between January 2001 and December 2015 at our tertiary care referral center were retrospectively analysed. The data was collected prospectively and radiology records of these patients were also searched. Those that became pregnant during the follow-up for BCS were included in the study. Patients in whom pregnancy occurred before BCS was diagnosed were excluded.

All patients were tested for the known prothrombotic factors. Combined oral contraceptive pill (OCP) use within the 3 mo preceding diagnosis of BCS was considered a thrombotic risk factor.

Where possible, patients had pre-pregnancy counselling and were made aware of the potential complications that may occur during pregnancy. Patients with known varices or portal hypertension had pre-pregnancy gastroscopy to ensure varices had been treated. These patients had further gastroscopies for variceal surveillance during second trimester. Patients with TIPSS had regular abdominal ultrasound to ensure patency of the TIPSS. The patients were monitored in a joint haematological/obstetric clinic.

Given the risk of embryopathy and fetal loss associated with warfarin, low molecular weight heparin (LMWH) was substituted for warfarin as soon as pregnancy was diagnosed, or prior to conception in one patient who had two *in-vitro* fertilisation treatments. The dose of LMWH was adjusted to maintain therapeutic factor Xa activity in selected cases under haematology supervision. LMWH treatment was replaced by warfarin following the delivery.

RESULTS

Baseline characteristics

Fifty-three female patients under follow-up for BCS were identified. Out of these, 7 patients had 16 pregnancies during the study period.

Median age of diagnosis of BCS was 25 years (range 21-34 years). Five (71%) patients had abdominal pain as the presenting complaint and symptoms were mainly chronic in nature. One patient had variceal haemorrhage and three patients had ascites on presentation of BCS. None of them had hepatic encephalopathy. None of the patients had other significant co-morbidities when the diagnosis of BCS was established. The characteristics of these patients including Rotterdam and Clichy scores at the time of diagnosis of BCS are given in Table 1. The laboratory values were stable at time of conception in all patients and ascites had resolved.

BCS was managed by anticoagulation therapy and radiological interventions with the aim to recanalise any outflow obstruction. Six out of the 7 patients underwent liver decompression procedures before conception. Procedures included dilatation of right hepatic vein (one patient), TIPSS (in four patients) and right hepatic vein stenting (one patient). One patient did not have any intervention for decompression and was managed with oral anticoagulation (warfarin) alone. All patients had anticoagulation. None of the patients in our series required surgical porto-systemic shunting or liver transplantation as a definite treatment of BCS.

At least one causal factor for hepatic vein obstruction was identified in 6 of these 7 women (86%). JAK 2V617F mutation alone was seen in 2 patients; factor V Leiden alone in one; JAK 2 mutation and factor V Leiden in one patient; JAK 2 mutation and OCP use in one patient; and factor V Leiden and OCP use in one patient**.** One patient did not have any identifiable risk factor.

Pregnancy course

Median age at conception was 32 years (range 23-39). Median time between diagnosis of BCS and conception was 5 years (range 3 mo-13 years). Follow up after the diagnosis of BCS in the seven women with pregnancies was for a median of 7 years (range 3-14 years). All patients that became pregnant had well compensated liver disease at the time of each conception and stigmata of decompensation of liver disease (ascites, in majority of patients at presentation) were no longer present at the time of any pregnancy. Gestational course is detailed in Table 2.

Aspirin (along with LMWH) was administered to one patient in 2 pregnancies (patient 6) for Essential Thrombocytosis. This patient was also treated with interferon for JAK 2 positive MPN. No patient was treated with beta-blockers during pregnancy.

Six out of the 16 (38%) pregnancies miscarried with fetal loss before 20 wk gestation. Six miscarriages/failed pregnancies occurred in 2 patients. One miscarried at 5 wk when she presented with vaginal bleeding. She was not aware of the pregnancy. The other patient had 5 miscarriages over a 9-year period. Two out of 5 were after the first trimester and these were attributed to cervical weakness and, therefore, she had cervical sutures in the following pregnancies (after 13 wk of gestation) leading to two successful deliveries.

Out of the 10 pregnancies reaching beyond 20 wk gestation, there were 3 vaginal deliveries and 7 caesarean sections. There was one very preterm birth at 27 wk and 5 preterm deliveries between 32 and 35 wk gestation, all with favourable neonatal outcomes. Four pregnancies resulted in delivery after 36-wk gestation, again all with favourable outcome.

Seven (70%) infants were delivered *via* emergency caesarean sections. Indications for caesarean section were varied, including fetal distress in three pregnancies; pre-eclampsia in one, breech presentation in one, bleeding from placenta praevia in one patient and difficult labour due to cervical suture in one patient.

Specific complications

Four patients developed intrahepatic cholestasis of pregnancy (ICP) in five pregnancies and they were treated with ursodeoxycholic acid. One patient had pre-eclampsia needing emergency caesarean section.

Table 1 Baseline characteristics of the patients at presentation

Patient ID	1	2	3	4	5	6	7
Age at diagnosis (yr)	34	21	30	21	31	24	25
Symptoms at presentation	Ascites	Oesophageal variceal haemorrhage, abdominal pain	Abdominal pain; ascites	Abdominal pain, ascites	Abdominal pain, fever, mouth ulcers	Ascites, renal failure and sepsis (ITU admission)	Abdominal pain
Risk factors for BCS	JAK 2 positive MPD; OCP	JAK 2 positive mutation	None identified	Factor V Leiden; OCP	JAK2 positive MPD (Essential Thrombocythaemia); Factor V Leiden	JAK 2 positive mutation	Factor V Leiden
Encephalopathy	None	None	None	None	None	None	None
Ascites	Moderate	Mild	Mild	Mild	None initially	Severe	Moderate
INR	1.7	1.4	1.2	1.3	1.7	1.4	1.5
Albumin (g/L)	28	37	49	49	49	25	26
Bilirubin (umol/L)	19	18	20	18	11	51	32
ALT (U/L)	-	31	-	57	-	-	-
AST (U/L)	134	49	20	34	27	277	43
Urea (mmol/L)	2.7	2.3	2.9	4.7	2.9	4.4	2
Creatinine (mmol/L)	72	43	70	68	51	92	70
Sodium (mmol/L)	143	137	143	142	140	130	133
MELD	19	14	6	10	12.37	14	17
UKELD	53	53	48	49	49	49	55
Hb (g/L)	137	121	155	128	150	147	88
WCC (10^9/L)	7.9	9.6	10.9	5.7	5.7	28.8	6.8
Platelets (10^9/L)	345	183	307	247	411	400	226
Rotterdam PI	1.116	0.072	1.12	0.07	1.08	1.244	1.168
Clichy PI	4.39	1.99	3.13	4.04	3.44	7.54	7.55
Liver biopsy	Not done	Not done	Not done	Suggestive of hepatic vein obstruction	Consistent with Hepatic venous outflow obstruction	Not done	Not done
Level of obstruction	Left hepatic vein	Hepatic vein	Hepatic vein	Hepatic Vein	Right Hepatic Vein	Left Hepatic vein	Hepatic vein
Radiological intervention	TIPSS	TIPSS	None	Angioplasty and Stenting to Hepatic vein	Right Hepatic Vein dilatation	TIPSS	TIPSS
Type of TIPSS	Viatorr (covered)	Viatorr (covered)	-	-	-	Memotherm, then Viatorr	Memotherm (Uncovered)
Medications post intervention	Warfarin	Warfarin	N/A	Warfarin	Warfarin	Warfarin, Interferon	Warfarin
Duration of follow up (yr)	4	5	7	3	13	14	14
Comments/ complications following intervention	TIPSS Stent redilatation after a week of insertion	TIPSS stent stenosis - needed to be re-dilated in 2 yr	Maintained on oral anticoagulation (warfarin) and did not require any intervention	Vascular Wallstent was re-canalized after 2 yr	Inferior RHV dilated 5 yr after the diagnosis (developed ascites and had compliance issues).	Bleeding from hepatic nodule (with INR > 9). Managed conservatively. Later stent was changed to a covered one for TIPSS stenosis	-

MPD: Myeloproliferative disorder; TIPSS: Trans-jugular intrahepatic posto-systemic shunt; OCP: Oral contraceptive pills; INR: International normalised ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MELD: Model for end-stage liver disease; UKELD: United Kingdom model for end-stage liver disease; Hb: Haemoglobin; WCC: White cell count.

Significant PV bleeding occurred after 3 pregnancies in 2 patients (patients 3 and 6 in Tables 1 and 2). One patient (patient 3) had a primary post-partum haemorrhage secondary to a retained placenta that was surgically removed. The other patient (patient 6) had a complicated first pregnancy with placental abruption at 27 wk gestation and needed emergency caesarean section. In her second pregnancy, she had secondary postpartum haemorrhage following caesarean section for suspected placental abruption. It was treated with surgical evacuation of uterine clot and insertion of a Rusch Balloon. There were no cases of variceal haemorrhage.

One patient, (patient 5) underwent regular gastroscopies for banding of (non-bleeding) oesophageal varices. That patient was not treated with beta-blockers during pregnancy. There were no cases of thrombosis in any of the pregnancies.

Table 2 Gestational course and perinatal complications in 16 pregnancies

Patient No.	Pregnancy No.	Age at gestation (yr)	Anticoagulation during pregnancy	Mode of delivery	Weeks gestation	Birth weight	Foetal/infant condition	Maternal condition
1	1	37	LMWH	Vaginal	36	2645 g	Neonatal jaundice, treatment with antibiotics for suspected infection	
2	2	24	LMWH	Emergency caesarean section	35	2140 g	Fetal distress (reduced foetal movements)- Healthy baby	ICP OGDs during pregnancy, no varices seen
3	3	35	LMWH	Vaginal delivery	35	2600 g	Mild Jaundice	*In-vitro* fertilization treatment
3	4	37	LMWH	Vaginal delivery	37	2450 g	Healthy	*In-vitro* fertilization treatment Primary post-partum haemorrhage secondary to retained placenta that was surgically evacuated
4	5	23	LMWH	Caesarean section	37	2645 g	Fetal distress - Healthy baby post delivery	…
5	6	36	LMWH and Aspirin (switched from warfarin and Hydroxyurea at 22 wk when pregnancy was diagnosed)	Emergency caesarean section	37	3115 g	Breech presentation	Had several gastroscopies (OGD) and banding to Oesophageal Varices during pregnancy
5	7	39	Warfarin	Miscarriage	5	-	-	PV bleeding; was not aware of conception
6	8	31	LMWH	Emergency Caesarean Section	27	Not available	Healthy boy	Bleeding secondary to placental abruption ICP from 25 wk
6	9	37	LMWH, Aspirin, interferon for MPD (Myeloproliferative disorder)	Emergency Caesarean section	35	Not available	Fetal distress. Healthy baby	ICP Minor subchorionic bleeding at 12 and 23 wk. LMWH reduced, aspirin stopped temporarily. Changes resolved on subsequent scans. Presentation with PH and suspected placental abruption at 35 wk Secondary post-partum haemorrhage treated with surgical of uterine clot evacuation and Rusch Balloon
7	10	25	LMWH	Miscarriage	9	-	-	-
7	11	27	LMWH	Miscarriage	20	-	Congenital pneumonia and mild amnionitis	Weakness of cervix;
7	12	28	LMWH	Miscarriage	19	-	-	Placental abruption Weakness of cervix; Placental abruption
7	13	29	LMWH	Emergency Caesarean Section	35	2974 g	Healthy boy	Dyspnoeic during 3rd Trimester; ICP in 20 wk onwards; C-Section for difficult labour (cervical suture could not be removed)
7	14	31	LMWH	Failed Pregnancy	10	-	-	Surgical removal of retained products of Contraception
7	15	33	LMWH	Miscarriage	7	-	-	-
7	16	34	LMWH	Emergency Caesarean Section	35	2440 g	Healthy boy	Pre-eclampsia; Breathlessness during 3rd trimester, PH diagnosed after pregnancy

LMWH: Low molecular weight heparin; ICP: Intrahepatic cholestasis of pregnancy; PH: Pulmonary hypertension.

Two patients (patients 6 and 7) developed symptoms of pulmonary hypertension (PH) during the

course of pregnancy and are described as follows.

Case 1

This patient had second pregnancy at the age of 37 years (13 years after the diagnosis and treatment of BCS). She had minor subchorionic bleeding noted on ultrasound during pregnancy. At 35 wk of gestation, this patient had emergency caesarean section for suspected placental abruption and developed respiratory failure post operatively. Trans-thoracic echocardiography (TTE) suggested PH with pulmonary artery systolic pressure estimated at 60-65 mmHg. CT scan excluded pulmonary embolism and showed patent TIPSS and mild splenomegaly. Right heart catheterisation confirmed the presence of PH with mean pulmonary artery pressure (mPAP) of 37 mmHg and pulmonary artery wedge (PAWP) pressure of 12 mmHg. She is being treated with Sildenafil (phosphodiesterase inhibitor) and Macitentan (endothelin receptor antagonist) for PH. Follow up investigations demonstrated improved exercise tolerance with no significant limitations in activities of daily living (patient 6; Tables 1 and 2).

Case 2

This patient delivered her second child at 34 years of age, 9 years after the diagnosis and treatment of BCS. Caesarean section was performed at 35-wk gestation for pre-eclampsia. Dyspnoea on exertion was noted during the pregnancy and six months after delivery she was admitted with right heart failure. CTPA excluded pulmonary embolus; but noted dilatation of pulmonary artery, moderate to severe dilatation of right atrium and moderate dilation of right ventricle with a degree of right ventricular hypertrophy. TIPSS was shown to be patent. TTE demonstrated severe PH, severely dilated right ventricle with impaired systolic function. Right heart catheterisation confirmed PH (mPAP 53 mmHg, PAWP 11 mmHg). The patient has been treated with sildenafil and intravenous Iloprost (along with warfarin) for PH and is being considered for lung transplantation assessment (patient 7; Tables 1 and 2).

DISCUSSION

The majority of the patients affected by BCS in Western countries are women of childbearing age[1,16], with the peak incidence in the third decade for women and in the fourth decade for men[17]. Fertility is generally unaffected in women with BCS as only a minority becomes cirrhotic.

Several previously reported observations suggest that pregnancy in BCS women could cause deterioration of the liver disease and pregnancy was associated with development of ascites in several women with known BCS[17-19]. Rautou *et al*[15] showed that the maternal outcome, in 14 women with 24 pregnancies is good in women becoming pregnant after the diagnosis and treatment of BCS. All mothers were alive at a median follow-up of 34 mo after last delivery and only one of them required liver transplantation after 73 mo follow-up.

In our series, there were no thrombotic events occurring during pregnancy or the postpartum period. This is comparable to previous study[15] where 2 of 17 pregnancies on anticoagulation therapy were complicated by portal vein thrombosis[15]. Subclavian and portal venous thrombosis has been reported in a pregnant patient with known and treated BCS secondary to (JAK 2 negative) essential thrombocytosis on anticoagulation[20].

Two patients had notable bleeding related to 3 deliveries in contrast to 6 patients with 7 bleeding episodes during pregnancy or postpartum in the previous study[15], signifying the importance of careful management of anticoagulation in pregnancy.

Both of our patients who developed pulmonary hypertension (mPAP $\geqslant$ 25 mmHg at rest) had the diagnosis of BCS and insertion of TIPSS several years ago. TIPSS has been regarded as a cardiac stress by suddenly increasing the preload leading to increased cardiac diastolic volumes and diameters, and a transient PH for 3-6 mo[21,22]. It is usually accommodated rapidly and is then associated with a reduction in systemic vascular resistance and a reduction in afterload[22]. However, development of PH after one and half years following TIPSS insertion has been reported[23]. In a recent study looking at the long-term cardiopulmonary outcome following TIPSS in cirrhotic patients, authors found higher prevalence of PH in the TIPSS group, 1 to 5 years post TIPSS implantation[24]. Although the patients in that study[24] could could have had associated cirrhotic cardiomyopathy, conversely there appears to be a potential long-term risk of development of PH in non-cirrhotic patients with a patent, functional TIPSS. Therefore, further studies on the interactions of TIPSS and cirrhotic cardiomyopathy are warranted[25].

PH has also been reported as a common finding in MPN[26]. This possible association of PH with MPN has also been suggested by small case series and studies[27-30] and the exact incidence and prevalence of PH in this group of patients remain poorly defined[31]. MPN could possibly have had an impact on the development of PH in one of our patients (patient 6).

Current recommendations are to offer endoscopic screening for varices in patients with portal hypertension, when conception is planned and during the second trimester if not already on prophylaxis. One patient (patient 2) who had originally presented with variceal haemorrhage underwent gastroscopy in second trimester for variceal screening and was found not to have varices. Another patient (patient 5, who had right hepatic vein dilatation) had several gastroscopies for oesophageal variceal band ligation during pregnancy. None of the patients suffered variceal bleeding during pregnancy or were administered non-selective beta-blockers during pregnancy given concerns regarding

use of beta-blockers in pregnancy[32,33].

The number of deliveries by caesarean section was higher in our group of patients (7 in 10 deliveries, 70%) than in the general obstetric population in England (26%)[34] and the previous study (8 caesarean sections in 17 pregnancies, 47%)[15]. Although some of the indications for caesarean section were clearly not related to the presence of BCS (*e.g.,* breech presentation, placenta praevia), the high incidence of placental disease (abruption, pre-eclampsia, fetal distress) leading to caesarean section may be related to the underlying causative aetiology of the BCS. Therefore, close maternal and fetal surveillance for placental disease should be considered in these patients.

Interestingly, for unknown reasons, incidence of ICP has been higher in our patients (4 patients in 5 pregnancies) than the normal obstetric population (0.7%-1.5%)[35,36].

Our study supports that the maternal outcome is good in women becoming pregnant after the diagnosis and treatment of BCS. This favourable maternal outcome is likely to be attributable to improvement in management of BCS including effective decompressive treatment, management of the underlying conditions, anticoagulant therapy with careful follow-up; and management of pregnancy and delivery in multi-disciplinary settings. A possibly decreased level of significant bleeding and no thrombosis implies the benefits of very close monitoring of anticoagulation through joint clinics.

In contrast to the good overall maternal outcome seen in our set of patients, the livebirth rate of 62.5% is lower than in the general obstetric population (84%[37] and 85%-88%[38]), but is better than earlier reports and in line with the finding of Rautou *et al*[15]. Importantly, failed pregnancies occurred in only 2 out of 7 patients. One patient (patient 7) had 5 fetal losses over a 9-year period (83% of the incomplete pregnancies reported here).

Our study supports the conclusion that BCS cannot be considered a contraindication to pregnancy in stable patients. Development of PH is an important finding that needs further validation. Such patients should be managed at tertiary level care centres with multi-disciplinary involvement.

COMMENTS

Background

Budd-Chiari syndrome (BCS) is a rare condition that results from hepatic venous outflow obstruction mainly due to the thrombosis of the hepatic veins and leading to hepatic dysfunction and portal hypertension. Patients with BCS usually have risk factors for venous thromboembolism (VTE). BCS mainly affects young women. Pregnancy is one of the risk factors for VTE and earlier studies reported that women with BCS could be at risk of developing severe exacerbation of BCS during their pregnancies.

Research frontiers

Pregnancy is an important issue in young women with known BCS. There are very few literature sources concerning the pregnancy related complications in women with known BCS. This study hotspot is to look at the outcome of pregnancies in women treated at the centre for BCS and to help other peers understand this important relationship.

Innovations and breakthroughs

Several previously reported observations suggest that pregnancy in women with BCS could cause deterioration of the liver disease. In this series, maternal outcome was good. There were no thrombotic events occurring during pregnancy or the postpartum period, comparable to a large previous study. Only two patients had notable bleeding related to 3 deliveries signifying the importance of careful management of anticoagulation in pregnancy. Two out of 7 patients developed pulmonary hypertension several years after the diagnosis of BCS and insertion of TIPSS. Higher prevalence of PH up to 5 years post TIPSS in cirrhotic patients has been reported recently. There appears to be a potential long-term risk of development of PH in non-cirrhotic patients with a patent, functional TIPSS that needs further exploration. There was higher incidence of deliveries by caesarean section (7 in 10 deliveries) in this study group and was attributed to the placental disease that could be related to the underlying causative aetiology of BCS.

Applications

This study supports that the maternal outcome in women becoming pregnant after the diagnosis and treatment of BCS is good. Fetal outcome beyond 20 wk gestation is also good. Close maternal and fetal surveillance for placental disease should be considered in these patients. Development of PH post TIPPS is an important finding that needs further validation. Such patients should be managed at tertiary level care centres with multi-disciplinary involvement.

Terminology

The BCS is named after a British Physician, George Budd in 1845 and a pathologist Hans Chiari who first described the features of BCS caused by the hepatic venous outflow obstruction in 1899. TIPSS-transjugular intrahepatic portosystemic shunt or transjugular intrahepatic portosystemic stent shunting is an artificial connection within the liver between the inflow portal vein and the outflow hepatic vein. This procedure is usually performed to reduce the portal pressure.

Peer-review

This is an interesting observational analysis of BCS in relation to pregnancy. Previous data are scarce and heterogeneous. The manuscript is nicely written.

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