ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2020 January 27; 12(1): 1-33

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

Contents

Monthly Volume 12 Number 1 January 27, 2020

World Journal of Hepatology
Volume 12 Number 1 January 27, 2020

Contents

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ke-Qin Hu, Koo Jeong Kang, Nikolaos T. Pyrsopoulos

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5182/editorialboard.htm

EDITORIAL OFFICE
Ruo-Yu Ma, Director

PUBLICATION DATE
January 27, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2020 January 27; 12(1): 1-5

DOI: 10.4254/wjh.v12.i1.1

ISSN 1948-5182 (online)

EDITORIAL

Meeting report of the editorial board meeting for *World Journal of Hepatology* 2019

Ruo-Yu Ma

ORCID number: Ruo-Yu Ma (0000-0002-2805-070X).

Author contributions: Ma RY contributed to organizing the editorial board meeting, making the meeting minutes, drafting and revising this manuscript.

Conflict-of-interest statement: Ma RY has nothing to disclose.

Manuscript source: Unsolicited manuscript

Received: December 10, 2019
Peer-review started: December 10, 2019
First decision: December 17, 2019
Revised: December 17, 2019
Accepted: December 19, 2019
Article in press: December 19, 2019
Published online: January 27, 2020

P-Reviewer: Citores MJ, Kagawa T, Kapoor S, Xiao J, Yuan YS
S-Editor: Yan JP
L-Editor: Filipodia
E-Editor: Wu YXJ

Ruo-Yu Ma, Editing and Publishing Development Department, Editorial Office, Baishideng Publishing Group Inc, Pleasanton, CA 94566, United States

Corresponding author: Ruo-Yu Ma, MSc, Director, Editing and Publishing Development Department, Editorial Office, Baishideng Publishing Group Inc, 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, United States. r.y.ma@wjgnet.com

Abstract

The first editorial board meeting of the *World Journal of Hepatology* (*WJH*) was held on November 8, 2019 at the Side Bar Grille, Sheraton Boston Hotel, Boston, MA, United States. Ruo-Yu Ma, Director of Editorial Office, on behalf of the Baishideng Publishing Group (BPG), organized the meeting with the great help of Professor Ke-Qin Hu, Journal Editor-in-Chief. There were six editorial board members, including two Editors-in-Chief and one administrative director of the editorial office at the meeting, discussing future strategies of the journal's development. The editorial board provided BPG a number of suggestions in regard to the business plan and quality control of the *WJH*. Regarding the business aspect, the editorial board suggested that BPG should advertise the *WJH* at the international Hepatology and Gastroenterology conferences and promote the *WJH via* social media. On the scientific aspect, the editorial board suggested that the assessment systems for managing the reviewers and the editorial board members are necessary, and that the BPG should make efforts to attract more high-quality manuscript submissions. An additional comment was to continue to foster a scientific culture for the journal. In conclusion, it was noted that these new ideas expressed during the meeting will bring the *WJH* to the next level. In the future, the BPG and the editorial board will increase communication and collaboration in order to further the development of the *WJH*.

Key words: Editorial board meeting; *World Journal of Hepatology*; Baishideng Publishing Group; Journal development; Quality control; Business plan

Core tip: The first editorial board meeting of the *World Journal of Hepatology* (*WJH*) was held on November 8, 2019 in Boston, MA, United States. During the meeting, the attendees discussed about the future strategy of the development of the *WJH*. Many new ideas, including for the business aspect and the scientific aspect, were proposed. Both the editorial office and the editorial board will make efforts based on this discussion to bring the *WJH* to the next level.

Citation: Ma RY. Meeting report of the editorial board meeting for *World Journal of Hepatology* 2019. *World J Hepatol* 2020; 12(1): 1-5
URL: https://www.wjgnet.com/1948-5182/full/v12/i1/1.htm
DOI: https://dx.doi.org/10.4254/wjh.v12.i1.1

INTRODUCTION

The first editorial board meeting of the *World Journal of Hepatology* (*WJH*) was called to order on November 8, 2019 at the Side Bar Grille, Sheraton Boston Hotel. It began at 19:00 and was presided over by Dr. Ke-Qin Hu, Journal Editor-in-Chief, with Ruo-Yu Ma, Director of Editorial Office, on behalf of Baishideng Publishing Group (BPG) as the organizer. The attendees discussed about how to develop the *WJH* and had a wonderful dinner.

ATTENDEES

There were seven attendees in total, including six editorial board members and one director of the editorial office. The editorial board members are: Dr. Ke-Qin Hu, Journal Editor-in-Chief; Dr. Nikolaos T Pyrsopoulos, Journal Editor-in-Chief; Dr. Calvin Pan, Associate Editor; and Dr. Astrid Ruiz-Margáin, Dr. Mohamed AS Kohla and Dr. Tatehiro Kagawa, Editorial Board. Ruo-Yu Ma, Director of Editorial Office, attended the meeting on behalf of the editorial office of BPG. Lian-Sheng Ma, CEO and Founder of BPG gave strong support for this meeting.

APPROVAL OF AGENDA

The meeting agenda was unanimously approved as distributed.

REPORTS

Self-introduction

After checking in, all the attendees briefly introduced their educational background, research field and their current work.

Opening

Dr. Hu explained that it was important for the *WJH* to hold an editorial board meeting, which would be very beneficial for the journal development. He was surprised that the journal had never held an editorial board meeting before, and thus he suggested Dr. Ma, the CEO of BPG, to organize this meeting during The Liver Meeting® 2019. With the great support from Dr. Ma and the BPG company, the editorial board meeting was called to order and held by Ruo-Yu Ma. He appreciated that the attendees could come to the meeting to follow the current situation of the *WJH* and to provide better support for the journal.

Overview of the WJH and BPG update

Ruo-Yu Ma summarized the current situation of the *WJH* and the BPG:

One hundred and seventy-six editorial board members from myriad countries across the globe contribute to the development of the journal. From its launch in 2009 to today in 2019, the *WJH* has published 1081 articles. Among these, the total cites is 13040 and the average cites per article is 12.1. The current number of total visits to the *WJH* homepage is about 1.6 million, of which 23% of those visits are from the United States and 21.4% from China. The *WJH* is now abstracted and indexed in PubMed, PubMed Central, ESCI, and major academic databases in China. BPG will submit an application to Clarivate Analytics in 2019, with anticipation of its being abstracted and indexed in SCIE.

BPG itself has 27 years of experience in editing and publishing medical journals. BPG currently publishes 43 clinical medical journals covering a wide range of topics, 7 of which are indexed in SCIE, 6 in ESCI (including the *WJH*), and 23 in PubMed and PubMed Central.

At the end of her presentation, Ruo-Yu Ma introduced her working experience in

BPG, welcomed the attendees and expressed her hope that new ideas would be proposed to bring the journal to the next level.

Open discussion

The attendees asked questions based on Ruo-Yu Ma's presentation, *e.g.*, the acceptance rate of the manuscript submitted, the time for peer reviewing and the indexing situation, and described their impression of the journal and their own experience of submitting and publishing manuscripts in the *WJH*. They proposed many good ideas on how to improve the scientific quality of the journal and how to enhance the impact and visibility. Dr. Pan pointed out that one of the major purposes of the meeting was to make the *WJH* abstracted and indexed in SCIE and gain a good impact factor (commonly known as the IF). The discussion was based mainly on the two aspects of developing a good journal: the business aspect and the academic aspect.

Editorial board's impression of the *WJH*: The editorial board thought that the *WJH* had been doing a good job but still had a long way to go. Dr. Ruiz-Margáin had submitted a manuscript to the *WJH*, and she said the software service was easy in general. The response from the reviewers was fast as well, which made her always like to submit manuscripts to the BPG journal series. According to Dr. Hu's experience, he thought that the submission process was a little cumbersome, because he spent more than an hour to deal with the guidelines and the files required. For clinicians who have very busy work, they would not like to spend plenty of time on the submission process. Dr. Pyrsopoulos also mentioned the importance of a user-friendly software.

Business plan of journal development: Dr. Pan first suggested that the major business of the *WJH* should be moved from China to the United States, because a majority of the Chinese scientists choose to publish in journals with IFs, while in the United States, scientists care more about whether the journal is indexed in PubMed. The shift of the focus may help to involve more active researchers.

Dr. Pyrsopoulos gave some good suggestions on how to advertise the journal and increase visibility based on his MBA background: (1) Advertisement in the conferences held in the United States, Europe and the Pacific, *e.g.*, to set a booth in the exhibition hall and the editorial board members who attend the meeting can help advertise. The editorial board suggested that BPG should attend the APASL2020 in March 2020. (2) Promoting the journal (*e.g.*, good manuscripts, editorial events) *via* social media, such as Facebook, Twitter and LinkedIn. Dr. Pyrsopoulos pointed out that BPG will attract plenty of followers through social networks. Dr. Ruiz-Margáin suggested that BPG can send a link of the manuscript to the author once the it is published so that the authors can share the link through social media. This will increase the cites of the published article as well.

Scientific aspect of journal development: The editorial board was very concerned about the quality control of the *WJH*. Based on the concern, Ruo-Yu Ma introduced the current tracking system for the assessment of the peer reviewers. Dr. Pan stressed the importance of the database to track the reviewers' performance. The quality of the journal is associated with the quality of the peer reviewers. The reviewers can neither be too picky nor too easy, actually, they should screen the manuscripts that meet the level of the *WJH*. The reviewers should write the peer-review report seriously and send the feedback timely. BPG can rate the peer reviewers according to their reviewing quality and only leave the high-quality reviewers in the database. The editorial board also suggested that 2-3 reviewers would be enough for reviewing a manuscript. The more reviewers are involved, the harder the decision will be made, and the authors will be confused as well.

Dr. Ruiz-Margáin noticed that many good reviews were published in the *World Journal of Gastroenterology* (*WJG*), and the *WJH* should invite highly influential reviews as well. For manuscript invitations, the editorial board suggested that BPG should raise the invitation threshold and should not reject the invited manuscripts. The list of the invited scientists should be previewed by the editors-in-chief and the associate editors, and the invited manuscript can be directly reviewed by the editorial board members for good quality control.

In order to expand the manuscript sources, BPG should "bend down" to pay for good manuscripts submitted to *WJH*, *e.g.*, to pay for language editing of the manuscripts with important scientific or clinical value. The journal should maintain a balance between making money to feed itself and improving the quality. Some manuscripts may not meet the level of the *WJG*; however, they may be good enough to be published in the *WJH*. These manuscripts should be transferred directly to the *WJH* for free. In this way, the *WJH* obtains good manuscripts while the authors will be

satisfied.

The attendees believed that 176 members are too many for the editorial board of the *WJH*. Therefore, it is very import to develop an assessment system for the editorial board performance. An annual report of the assessment should be sent to every editorial board member so that they will be encouraged by what they have done and will contribute more actively in the future. BPG can also award the board members for their contribution. Besides, BPG can launch a newspaper for the editorial board members, to let them know the updates of the *WJH* and BPG. The scale of the editorial board should be downsized to around 50 people for a better management and quality control. Those who neither review the manuscripts nor publish their work in the *WJH* should be removed from the editorial board.

Culture of the journal: The minor comment from the editorial board is to cultivate a culture for the *WJH*. Since there is an article processing charge for publishing in the *WJH*, the editorial board suggested that the fee should be discounted for authors from low-income countries and young fellows without financial support. These young fellows will appreciate the journal for helping them publish their articles and will contribute more good work to the journal in the future. Encouraging the young fellows to publish their good work can form a good culture of the *WJH*.

At the end of the discussion, Dr. Pan summarized the efforts that should be made for the development of the *WJH*: (1) Quality assessment of the reviewers and the editorial board members; (2) A more user-friendly online system; and (3) Successful marketing. Dr. Pan expressed his hope that the *WJH* should receive the first IF within 2 years.

Wrap up

Dr. Hu summarized the editorial board meeting and expressed his gratitude to all the attendees for presenting new ideas for journal development. All the attendees took a group photo before leaving (Figure 1). The photo has been posted on the Twitter of BPG.

CONCLUSION

This was the first editorial meeting of the *WJH*, during which many good ideas were proposed. The BPG office has already made some attempts based on this meeting: (1) An official BPG Twitter account has been registered, which will be an advertising platform for the "World Journal" series in the future; and (2) From January 1, 2020, the publication fee will be discounted by 25% for the manuscripts supported by national/international funds and those contributed by current national/international association/society members. The editorial office will hold an internal meeting in regard to the detailed plan and timeline to roll out the new initiatives. The BPG and the editorial board should work more closely to improve both the business and the scientific quality of the *WJH*. In the future, the editorial board meeting should be organized regularly and, hopefully, more BPG staff as well as the editorial board members will be involved in the communication.

Figure 1 Group photo of the editorial board meeting for *World Journal of Hepatology* 2019. From left to right: Ruo-Yu Ma, Dr. Tatehiro Kagawa, Dr. Mohamed AS Kohla, Dr. Ke-Qin Hu, Dr. Nikolaos T Pyrsopoulos, Dr. Astrid Ruiz-Margáin, and Dr. Calvin Pan.

ACKNOWLEDGEMENTS

The BPG wants to express our sincere gratitude to the editorial board members who attended the first editorial board meeting as well as all the other members who have made efforts for the development of the *WJH*.

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2020 January 27; 12(1): 6-9

DOI: 10.4254/wjh.v12.i1.6

ISSN 1948-5182 (online)

MINIREVIEWS

Concise review of machine perfusion in liver transplantation

Chirag S Desai, David A Gerber

ORCID number: Chirag S Desai (0000-0002-3784-0973); David A Gerber (0000-0002-7972-5228).

Author contributions: Gerber DA performed the review and wrote the paper; Desai CS wrote the paper.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Manuscript source: Unsolicited manuscript

Received: September 1, 2019
Peer-review started: September 1, 2019
First decision: September 20, 2019
Revised: November 21, 2019
Accepted: November 29, 2019
Article in press: November 29, 2019
Published online: January 27, 2020

P-Reviewer: Enosawa S, Ferrigno A, Gavriilidis P, Hori T, Nacif L
S-Editor: Ma RY
L-Editor: A
E-Editor: Wu YXJ

Chirag S Desai, David A Gerber, Department of Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, United States

David A Gerber, Lineberger Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, United States

Corresponding author: David A Gerber, MD, Professor, Department of Surgery, University of North Carolina at Chapel Hill, CB#7211, 4025 Burnett-Womack Building, Chapel Hill, NC 27599, United States. david_gerber@med.unc.edu

Abstract

With the advances and clinical growth in liver transplantation over the last four decades the focus on expanding deceased donor organs has been in need of scientific research. In the past ten years several researchers have looked at the domain of machine perfusion as it applies to deceased donor livers. The following review focuses on the clinical trials and recent advances that will likely have the earliest entrance into the clinical arena.

Key words: Liver transplantation; Machine perfusion; *Ex vivo* perfusion; Ischemia reperfusion; Organ preservation

Core tip: The processes involved in optimizing and expanding the deceased donor liver pool has led to the incorporation of machine perfusion technologies (as is similarly done in kidney transplantation). While none of the systems is approved for clinical use, several have gone through clinical trials. This summary provides an overview of those technologies that are likely to be used in clinical liver transplantation.

Citation: Desai CS, Gerber DA. Concise review of machine perfusion in liver transplantation. *World J Hepatol* 2020; 12(1): 6-9
URL: https://www.wjgnet.com/1948-5182/full/v12/i1/6.htm
DOI: https://dx.doi.org/10.4254/wjh.v12.i1.6

INTRODUCTION

Clinical advances in liver transplantation over the last three decades have resulted in

more than 10000 liver transplants being performed annually throughout the world, with 1- and 5-year patient survival outcomes in excess of 90% and 70%, respectively[1]. Unfortunately, the increasing incidence of liver disease amongst the general population[2] is contributing to a growing discrepancy between the number of transplantable organs and the number of patients on the liver transplant waitlist. To expand the donor pool requires using marginal donor organs [*i.e.*, donation after cardiac death (DCD) *vs* brain dead donors (DBD), fatty livers or livers from the elderly with multiple co-morbidities][1]. The consequence of ischemia/reperfusion injury (IRI) in these marginal donor allografts includes an increased rate of primary non-function, early graft dysfunction, biliary complications, decreased long-term graft survival, and increased hospital resource use after transplantation[3]. Strategies to minimize IRI involve focusing on organ preservation techniques. Static cold storage (SCS) is the standard approach to preserve the liver during transit from the donor to the potential recipient. During the last decade machine perfusion has been investigated as a method to modulate liver preservation, improving the function of less optimal grafts, and potentially resuscitating some grafts that previously would have been deemed unsuitable for transplant[4].

While the history of organ perfusion systems goes back decades the first clinical trial of hypothermic machine perfusion (HMP) of the liver was carried out in 2009 by Guarrera *et al*[5] and it provided evidence of the safety and efficacy of HMP by reducing levels of transaminases and total bilirubin. In a follow-up study the investigators showed that HMP provided safe and reliable preservation in 31 adults undergoing liver transplantation when the organ had previously been declined by other transplant centers[6]. In 2014, hypothermic oxygenation machine perfusion (HOPE) was introduced in a study with donors who were DCD rather than DBD. This study showed that the outcome of DCD liver transplantation after HOPE conditioning was comparable to matched DBD liver grafts in terms of liver transaminases [aspartate aminotransferase/alanine aminotransferase (AST/ALT)], intensive care unit admission and hospital stay, while costs during hospital stay were significantly lower[7]. This same group carried out a larger clinical trial (n = 25) and found that HOPE conditioning of DCD livers significantly reduces graft injury with regard to peak ALT, biliary complications, graft failure and 1-year graft survival compared to SCS[4,8].

The development of normothermic machine perfusion (NMP) as an alternative MP approach led to a 2016 clinical trial with 20 patients[9]. Seven-day median peak AST after transplantation was significantly lower in the NMP group compared to SCS, demonstrating the safety and feasibility of NMP for organ retrieval, transport and transplantation. In 2016, Selzner *et al*[10] showed that grafts preserved by NMP had lower liver transaminase levels 1–3 d after transplantation, but this result was not statistically different compared with SCS. Similar to what was found in the HMP studies, a 2017 study using NMP enabled assessment and transplantation of 12 livers previously declined for transplant, suggesting that avoiding hypoxia during perfusion prevents post-perfusion syndrome and monitoring biliary pH could predict postoperative cholangiopathy[11]. The largest clinical trial to date was coordinated through the Consortium for Organ Preservation in Europe. In a multi-center, randomized control trial involving 220 adult DBD and DCD donors normothermic preservation is associated with a 50% lower level of graft injury, measured by hepatocellular enzyme release, despite a 54% longer mean preservation time and an expanded donor pool (50% lower rate of organ discard). There was no significant difference in bile duct complications, graft survival or patient survival. In summary, this study successfully proves the investigators' primary endpoint of lower peak serum AST levels in the NMP group implying a benefit in livers used for transplantation[1]. A summary of the clinical trials to date is presented in Table 1[3,5,6,8,12,13].

With the increasing prevalence of obesity, a growing number of livers with macrosteatosis will be considered for transplant. A major area where machine perfusion will be useful involves a defatting strategy. The aim of this strategy is to reduce the triglyceride load in steatotic hepatocytes, improve the organ metabolism and lessen the impact of ischemia-reperfusion injury. Machine perfusion reduces intracellular lipids by enhancing lipid metabolism, lipolysis and increasing the cellular exportation of intracellular triglyceride as very lowdensity lipoprotein and the fatty acid mitochondrial βoxidation; when used in conjunction with defatting agents[14,15]. This process helps to lower the production of reactive oxygen species, decreased cellular injury and improved microcirculation.

Table 1 Machine perfusion in human liver transplantation

Ref.	Experimental group (*n*)	MP time (h)	Device
Guarrera *et al*[6], 2015	31	3.8	Hypothermic MP
Dutkowski *et al*[8], 2015	25	2	Hypothermic oxygenated MP
Bral *et al*[12], 2017	9	11.5	Normothermic MP
Ravikumar *et al*[13], 2016	20	9.3	Normothermic MP
Selzner *et al*[10], 2016	10	8	Normothermic MP
Nasralla *et al*[1], 2018	121	9.13	Normothermic MP

MP: Machine perfusion.

CONCLUSION

Machine perfusion (Figure 1) has the potential to transform the field of liver transplantation by allowing clinicians to expand the donor pool while reconditioning the organ prior to implantation.

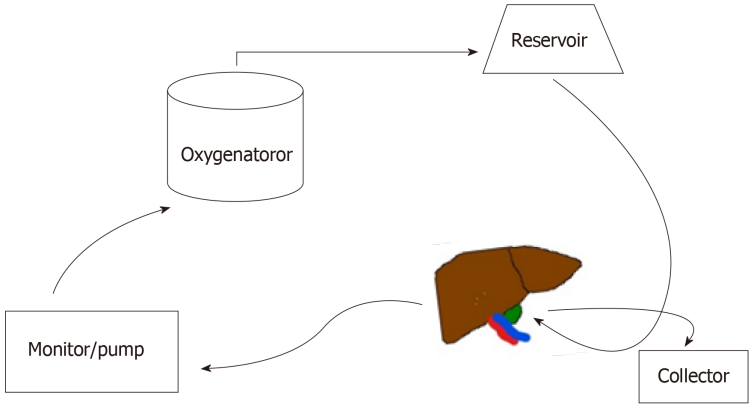

Figure 1 Schematic design of machine perfusion. Demonstrating system circulation and pumps with the ability to oxygenate the perfusate. Flow comes into the liver through the portal vein with bile collected separately.

REFERENCES

1 **Nasralla D**, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL, Chiocchia V, Dutton SJ, García-Valdecasas JC, Heaton N, Imber C, Jassem W, Jochmans I, Karani J, Knight SR, Kocabayoglu P, Malagò M, Mirza D, Morris PJ, Pallan A, Paul A, Pavel M, Perera MTPR, Pirenne J, Ravikumar R, Russell L, Upponi S, Watson CJE, Weissenbacher A, Ploeg RJ, Friend PJ; Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018; **557**: 50-56 [PMID: 29670285 DOI: 10.1038/s41586-018-0047-9]

2 **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: 26707365 DOI: 10.1002/hep.28431]

3 **Quillin RC**, Guarrera JV. Hypothermic machine perfusion in liver transplantation. *Liver Transpl* 2018; **24**: 276-281 [PMID: 29278454 DOI: 10.1002/lt.25004]

4 **Jia JJ**, Li JH, Yu H, Nie Y, Jiang L, Li HY, Zhou L, Zheng SS. Machine perfusion for liver transplantation: A concise review of clinical trials. *Hepatobiliary Pancreat Dis Int* 2018; **17**: 387-391 [PMID: 30352672 DOI: 10.1016/j.hbpd.2018.06.003]

5 **Guarrera JV**, Henry SD, Samstein B, Odeh-Ramadan R, Kinkhabwala M, Goldstein MJ, Ratner LE, Renz JF, Lee HT, Brown RS, Emond JC. Hypothermic machine preservation in human liver transplantation: the first clinical series. *Am J Transplant* 2010; **10**: 372-381 [PMID: 19958323 DOI: 10.1111/j.1600-6143.2009.02932.x]

6 **Guarrera JV**, Henry SD, Samstein B, Reznik E, Musat C, Lukose TI, Ratner LE, Brown RS, Kato T, Emond JC. Hypothermic machine preservation facilitates successful transplantation of "orphan" extended criteria donor livers. *Am J Transplant* 2015; **15**: 161-169 [PMID: 25521639 DOI: 10.1111/ajt.12958]

7 **Dutkowski P**, Schlegel A, de Oliveira M, Müllhaupt B, Neff F, Clavien PA. HOPE for human liver grafts obtained from donors after cardiac death. *J Hepatol* 2014; **60**: 765-772 [PMID: 24295869 DOI: 10.1016/j.jhep.2013.11.023]

8 **Dutkowski P**, Polak WG, Muiesan P, Schlegel A, Verhoeven CJ, Scalera I, DeOliveira ML, Kron P, Clavien PA. First Comparison of Hypothermic Oxygenated PErfusion Versus Static Cold Storage of Human Donation After Cardiac Death Liver Transplants: An International-matched Case Analysis. *Ann Surg* 2015; **262**: 764-70; discussion 770-1 [PMID: 26583664 DOI: 10.1097/SLA.0000000000001473]

9 **Leithead JA**, Armstrong MJ, Corbett C, Andrew M, Kothari C, Gunson BK, Muiesan P, Ferguson JW. Hepatic ischemia reperfusion injury is associated with acute kidney injury following donation after brain death liver transplantation. *Transpl Int* 2013; **26**: 1116-1125 [PMID: 24033747 DOI: 10.1111/tri.12175]

10 **Selzner M**, Goldaracena N, Echeverri J, Kaths JM, Linares I, Selzner N, Serrick C, Marquez M, Sapisochin G, Renner EL, Bhat M, McGilvray ID, Lilly L, Greig PD, Tsien C, Cattral MS, Ghanekar A, Grant DR. Normothermic ex vivo liver perfusion using steen solution as perfusate for human liver transplantation: First North American results. *Liver Transpl* 2016; **22**: 1501-1508 [PMID: 27339754 DOI: 10.1002/lt.24499]

11 **Mourad MM**, Algarni A, Liossis C, Bramhall SR. Aetiology and risk factors of ischaemic cholangiopathy after liver transplantation. *World J Gastroenterol* 2014; **20**: 6159-6169 [PMID: 24876737 DOI: 10.3748/wjg.v20.i20.6159]

12 **Bral M**, Gala-Lopez B, Bigam D, Kneteman N, Malcolm A, Livingstone S, Andres A, Emamaullee J, Russell L, Coussios C, West LJ, Friend PJ, Shapiro AM. Preliminary Single-Center Canadian Experience of Human Normothermic Ex Vivo Liver Perfusion: Results of a Clinical Trial. *Am J Transplant* 2017; **17**: 1071-1080 [PMID: 27639262 DOI: 10.1111/ajt.14049]

13 **Ravikumar R**, Jassem W, Mergental H, Heaton N, Mirza D, Perera MT, Quaglia A, Holroyd D, Vogel T, Coussios CC, Friend PJ. Liver Transplantation After Ex Vivo Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial. *Am J Transplant* 2016; **16**: 1779-1787 [PMID: 26752191 DOI: 10.1111/ajt.13708]

14 **Nagrath D**, Xu H, Tanimura Y, Zuo R, Berthiaume F, Avila M, Yarmush R, Yarmush ML. Metabolic preconditioning of donor organs: defatting fatty livers by normothermic perfusion ex vivo. *Metab Eng* 2009; **11**: 274-283 [PMID: 19508897 DOI: 10.1016/j.ymben.2009.05.005]

15 **Taba Taba Vakili S**, Kailar R, Rahman K, Nezami BG, Mwangi SM, Anania FA, Srinivasan S. Glial cell line-derived neurotrophic factor-induced mice liver defatting: A novel strategy to enable transplantation of steatotic livers. *Liver Transpl* 2016; **22**: 459-467 [PMID: 26714616 DOI: 10.1002/lt.24385]

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2020 January 27; 12(1): 10-20

DOI: 10.4254/wjh.v12.i1.10

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Lessons from "real life experience" of rifaximin use in the management of recurrent hepatic encephalopathy

Fiona Chautant, Maeva Guillaume, Marie-Angèle Robic, Jean-François Cadranel, Jean-Marie Peron, Hortensia Lison, Charlène Cool, Christophe Bureau, Véronique Duhalde

ORCID number: Fiona Chautant (0000-0001-9679-4674); Maeva Guillaume (0000-0002-2782-7556); Marie-Angèle Robic (0000-0002-9540-2322); Jean-François Cadranel (0000-0002-8442-4526); Jean-Marie Péron (0000-0002-0510-8577); Hortensia Lison (0000-0002-9620-7449); Charlène Cool (0000-0002-7436-1568); Christophe Bureau (0000-0001-8634-9278); Véronique Duhalde (0000-0001-7627-951X).

Author contributions: Chautant F was the guarantor of the article; Chautant F, Bureau C and Duhalde V designed the research study; all authors were involved with data collection or analysis; all authors were involved with data interpretation, drafting or offering critical revisions; Bureau C and Chautant F performed statistical analyses; all authors have read and approved the final manuscript.

Institutional review board statement: As a retrospective study, the approval of the ethics committee was not mandatory (*i.e.*, according to the Jardé Law in France).

Informed consent statement: Informed consent was not required for this study. The data were collected anonymously.

Conflict-of-interest statement: Bureau C and Cadranel JF have conflicts of interest with Alpha Wassermann as speakers at a symposium and Norgine as consultants. The remaining authors

Fiona Chautant, Service Pharmacie, Centre Hospitalier Universitaire de Toulouse, Hôpital Paule de Viguier, Toulouse 31059, France

Maeva Guillaume, Marie-Angèle Robic, Jean-Marie Peron, Christophe Bureau, Department of Hepato-Gastroenterology, University Hospital, Toulouse 31059, France

Jean-François Cadranel, Hortensia Lison, Department of Hepato-Gastroenterology, Laennec Hospital, Creil 60109, France

Charlène Cool, Department of Pharmacy and UMR INSERM 1027, University Hospital, Toulouse 31059, France

Véronique Duhalde, Department of Pharmacy, University Hospital Toulouse, Toulouse 31059, France

Corresponding author: Fiona Chautant, PhD, Pharmacist, Department of Pharmacy, University Hospital, 330 avenue de Grande Bretagne, Toulouse 31059, France.
fiona.chautant@gmail.com

Abstract

BACKGROUND

Hepatic encephalopathy (HE) is a major complication of cirrhosis with independent prognostic significance. The current management of HE is mainly based on lactulose. Rifaximin has been shown to decrease the risk of HE recurrence in patients with episodic forms. HE can also be persistent. However, there is no drug support recommendation for rifaximin use in this setting.

AIM

To assess the effectiveness of rifaximin in the management of recurrent episodes of HE and recurrent acute exacerbations on persistent HE, in "real life conditions".

METHODS

In this retrospective study, using a within-subjects design, we collected data of patients treated with rifaximin for HE in two liver diseases centers, during the six-month period before and during the six-month period after the initiation of rifaximin. The primary effectiveness endpoint was the total number of HE events involving hospitalization.

RESULTS

disclose no conflict.

Manuscript source: Unsolicited manuscript

Received: July 1, 2019
Peer-review started: July 1, 2019
First decision: August 7, 2019
Revised: September 30, 2019
Accepted: December 8, 2019
Article in press: December 8, 2019
Published online: January 27, 2020

P-Reviewer: Abd-Elsalam S, García-Compeán D, Thompson RR
S-Editor: Ma YJ
L-Editor: A
E-Editor: Wu YXJ

Rifaximin was introduced for prevention of recurrent HE episodes in 29 out of 62 patients with normal mental status between episodes and for prevention of recurrent acute exacerbations on persistent HE in 33 out of 62 patients. In the "prevention of recurrent HE episodes" group, fewer HE events (0.79 *vs* 1.78; P = 0.013) were reported during the period of time when rifaximin was used. In the "prevention of recurrent acute exacerbations on persistent HE" group, there was no significant difference in the number of HE-events (1.48 *vs* 1.77; P = 0.582).

CONCLUSION
In this real-life experience, the effectiveness of rifaximin was confirmed in the prevention of HE episodes recurrence but was not proved in the prevention of acute exacerbations recurrence on persistent HE.

Key words: Rifaximin; Hepatic encephalopathy; Cirrhosis; Liver disease; Hospitalization

Core tip: The clinical and economic burdens of hepatic encephalopathy (HE) are tremendous and growing worldwide. Therapies to improve the quality of life of patients and to decrease the rate of hospitalizations and economic consequences are needed. Rifaximin was proved effective to reduce the risk of HE recurrence in patients with episodic forms. However, real-life data are still scarce, particularly concerning persistent HE. In this real-life experience, the effectiveness of rifaximin was confirmed in the prevention of HE episodes recurrence but was not proved in the management of persistent HE.

Citation: Chautant F, Guillaume M, Robic MA, Cadranel JF, Peron JM, Lison H, Cool C, Bureau C, Duhalde V. Lessons from "real life experience" of rifaximin use in the management of recurrent hepatic encephalopathy. *World J Hepatol* 2020; 12(1): 10-20
URL: https://www.wjgnet.com/1948-5182/full/v12/i1/10.htm
DOI: https://dx.doi.org/10.4254/wjh.v12.i1.10

INTRODUCTION

Cirrhosis is the final stage of most chronic liver diseases and is the fourth most common cause of death in Europe, accounting for 170000 deaths per year against 33539 in the United States and 1.03 million worldwide[1]. The exact prevalence of cirrhosis is unknown. It is estimated between 0.1% to 0.27% in the European[2] and United States populations[3].

Hepatic encephalopathy (HE) is a frequent and major complication of cirrhosis. HE is estimated to affect 30%-40% of patients with cirrhosis at some time during their clinical course[4]. HE impairs daily functioning and health-related quality of life (HRQL) of cirrhotic patients[5] and is associated with a high risk of recurrence. Episodes of HE are associated with residual effects on cognitive functions[6] and are frequently associated with hospitalizations[7]. Frequent occurrence of HE and high hospital admission rates result in a significant economic burden to healthcare systems[8]. HE affects the patients' survival and constitutes an important prognostic factor[9,10] with a 1-year survival rate of 40% to 50% and a 3-year survival rate of approximately 20%[11,12]. Therefore, the prevention of HE is a major objective in the management of cirrhotic patients.

Current therapeutic approaches for HE treatment and prevention aim at reducing the production or intestinal absorption of ammonia. Lactulose, a nonabsorbable disaccharide, is the first line treatment of HE[4]. Some poorly absorbed antibiotics, such as neomycin or vancomycin, have proven to be effective. Their use has been limited by an increased risk of antimicrobial resistance and/or severe adverse effects[13,14].

Rifaximin, a minimally absorbed oral antibiotic, appears to have a better profile and aims at decreasing intestinal ammonia production. This antibiotic may also reduce the bacterial translocation involved in inflammation in HE[15]. An antiprotozoal, nitazoxanide also showed interesting results in association with lactulose[16]. Furthermore, rifaximin treatment could be an alternative to norfloxacin in secondary prevention of spontaneous bacterial peritonitis, another complication of liver

cirrhosis[17].

In 2010, the efficacy of rifaximin has been reported for preventing episodes of HE in patients with an history of recurrent HE[18]. The use of rifaximin also improved HRQL in patients with cirrhosis and recurrent HE[19]. On the contrary, the literature data are inconclusive concerning the management of persistent HE and are scarce in real life conditions. In this study we described the use of rifaximin and assessed the effectiveness of rifaximin in the management of HE in "real life".

This approach is very important as real-life data are relatively scarce and can be much different compared to randomized studies as underlined by Krag *et al*[20] in the PROSPER multicenter observational study.

MATERIALS AND METHODS

Study design and population

We performed a retrospective study conducted in two liver diseases centers in France; one is an academic hepatology center (Toulouse) and the other is a primary referral hospital with high expertise in chronic liver diseases and cirrhosis (Creil).

All cirrhotic patients with HE treated with rifaximin were considered for inclusion. The inclusion period ranged from July 1, 2010 to September 13, 2013, according to the French temporary authorization for rifaximin use. For each patient, the date of inclusion corresponded to the initiation of rifaximin treatment.

The following parameters were collected at inclusion. We considered anamnestic data: Gender, age, etiology of cirrhosis, medical history (HE, gastrointestinal bleeding, ascites, renal failure and hepatocellular carcinoma), presence of a transjugular intrahepatic portosystemic shunt (TIPS), smoking and/or active alcoholism; anthropometric and biochemical data.

The study period included the six months before the initiation of treatment with rifaximin (period 1: "without rifaximin") up to six months or until the end of treatment (period 2: "with rifaximin"). This treatment duration was chosen from the pivotal study schedule[18]. Each patient served as his or her own control. The period "without rifaximin" was used as the reference period for assessing the effectiveness of rifaximin.

For each period, clinical characteristics were recorded: The number of hospitalizations for HE, number of HE events during hospitalization, cumulative time of HE-related hospitalization, grade of HE (according to the West Haven Criteria[21]), the presence or absence of the main precipitating factors of HE described in the literature factors, occurrence of bacterial infections. The recurrent and persistent character of HE was specified, according to the time course of HE.

Recurrent HE is a term used when episodes occur within a time frame of 6 mo or less. Persistent HE denotes a pattern of behavioral alterations such as depressive mood, mild anxiety and/or difficulties to sleep at night that are always present interspersed with relapses of HE[4]. Therefore, in addition to persistent HE, acute exacerbations are noticed[22]. We have considered as recurrent HE either when confronted to a recurrence of HE episodes or to a recurrence of acute exacerbations on persistent HE. The characteristics related to rifaximin treatment were also considered: Indication, dosage, duration, cause of interruption, occurrence of adverse effects, and concomitant use of lactulose. The indication was based on data collected during the period without rifaximin and was not modified during the 6-mo follow up with rifaximin.

Data were collected for the two periods using hospitalization and consultation reports via electronic medical records in the same way. The clinical description of HE is based on a non-standardized evaluation. It depends on the physical examination by a senior hepato gastroenterologist according to the West-Haven criteria.

The primary effectiveness endpoint of the study was the total number of HE events during the period of hospitalization; the HE events corresponded to episodes of HE and acute exacerbations in patients with a persistent form.

The secondary endpoints were the number of HE-related hospitalizations, the length of HE-related hospitalization, the probability of HE recurrence among patients in remission from HE episodes, the probability of persistent HE cessation, occurrence of bacterial infections, safety and predictive factors of response to treatment. HE-related hospitalizations corresponded to hospitalizations with a diagnosis of HE; length of hospitalization: Total duration of hospital stay. The presence of predictive factors of response to treatment was assessed by comparing clinical and biological parameters collected at baseline between patients who responded to rifaximin therapy and patients who did not. The response to treatment was defined as the cessation of persistent HE or maintenance of remission from recurrent HE among patients in

remission from episodes of HE. Some results were considered for the entire cohort and for two subgroups of patients, "prevention of recurrent HE episodes" and "prevention of recurrent acute exacerbations on persistent HE".

In order to ensure optimal comparison to evaluate the effectiveness and tolerance of rifaximin between the two periods, all data presented were assessed by taking into account the follow-up time. The results were expressed within 100 d of follow-up. As a retrospective study, the approval of the ethics committee was not mandatory (*i.e.*, according to the Jardé Law in France). It did not require a consent from patients as the study analyzed data from usual care during hospitalization. The patients' data were made anonymous prior to analysis.

Statistical analysis

Qualitative variables have been described by the number and the percentage of each modality. They were compared using McNemar's chi-square tests or with Fisher exact tests (for expected values < 5). Quantitative variables were described by mean ± SD and were compared using Student's *t*-test for paired samples. For all tests, a significant level of 0.05 was considered. Kaplan-Meier methods were used to estimate the probability of HE recurrence and cessation of persistent HE. A statistical analysis was performed with SPSS software, version 19.0 (Chicago, IL, United States).

RESULTS

Study population

Sixty-two patients were included, with a sex ratio male/female of 2.6 and an average age of 62 ± 10 years. The cause of cirrhosis was alcohol in 41 (66%), hepatitis B or C in 16 (26%), non-alcoholic fatty-liver disease in 10 (16%), other causes in 7 (11%); combined etiologies were found in 12 patients (19%). The HE events occurring six months before the introduction of rifaximin therapy were described. A recurrent HE was observed for about half of the patients (55%). The majority of the patients (68%) has been hospitalized several times for HE (Table 1).

Therapeutic care

During period 1, 53 patients (85.5%) received lactulose therapy (average dose, 37 ± 18 g/d; range, 10-90 g/d) compared to 52 patients (83.9%) during period 2, (average dose, 42 ± 22 g/d; range, 10-90 g/d). The average dose of rifaximin therapy during period 2 was 1000 mg/d for 54 patients (87%) and 1200 mg/d for 8 patients (13%). Rifaximin was prescribed according to two indications: Prevention of recurrent acute exacerbations on persistent HE in 33 patients (53%) and prevention of recurrent HE episodes in 29 patients (47%). Thirty-four patients (55%) received rifaximin therapy for at least six months. A treatment discontinuation was observed in 24 patients (39%). The causes were: death (n = 7), liver transplantation (n = 5), improvement of symptoms (n = 4), lack of clinical improvement (n = 3), non-compliance (n = 3), adverse effect (n = 1) and palliative care (n = 1). A temporary and voluntary interruption of treatment was observed in 4 patients with an average duration of 33.2 d. During this 6-mo follow-up, the average duration of rifaximin therapy was 143 d (range, 7-180 d).

Rifaximin effectiveness

In the whole cohort, we observed a downward trend in the total number of HE-events, in the number of HE-related hospitalizations, and in the length of hospital stay between periods 1 and 2 (Figure 1A).

For the subgroup "prevention of recurrent HE episodes" (Figure 1B), the total number of HE events (0.79 *vs* 1.78; P = 0.013), the number of HE-related hospitalizations (0.75 *vs* 1.57; P = 0.030) and the length of HE-related hospitalization (6.98 d *vs* 15.71 d; P = 0.027) were significantly lower during the period with rifaximin compared to the period without rifaximin.

When rifaximin was given for prevention of recurrent acute exacerbations on persistent HE, there was a non-significant increase in the number of HE events (1.77 *vs* 1.48) and in the length of hospitalization (24.67 d *vs* 18.05 d). The number of HE-related hospitalizations decreased between the two periods (1.15 *vs* 1.25; P = 0.728) but the difference was not significant (Figure 1C).

Appearance of the first recurrence of an HE episode in patients with remission

The probability of HE recurrence was 46% among patients in remission from HE episodes during rifaximin therapy. The median time to the first HE occurrence was 118.5 d (95%CI: 91.8-145.3) (Figure 2).

Table 1 Baseline characteristics of study patients (*n* = 62)

Demographic characteristics	
Age, mean ± SD, yr	62 ± 10
Male sex, *n* (%)	45 (73)
Cirrhosis etiology, *n* (%)	
Alcohol	41 (66)
Alcohol withdrawal, *n* (%)	34/41 (83)
Hepatitis-B or C virus	16 (26)
Non-alcoholic fatty liver disease	10 (16)
Other	7 (11)
Previous liver related complication, *n* (%)	
HE	62 (100)
Gastrointestinal bleeding	28 (45)
Ascites	39 (63)
Renal failure	24 (39)
Hepatocellular carcinoma	14 (23)
Presence of oesophageal varices	48 (77)
TIPS, *n* (%)	25 (40)
Scores	
Child class, *n*	
A/B/C	2/36/24
Child score, mean ± SD	9.2 ± 2.0
MELD, mean ± SD	16.8 ± 6.4
Total number of HE events occurred in hospitalization or requiring hospitalization, *n* (%)	
0	1 (2)
1	16 (26)
2	17 (27)
> 2	28 (45)
The highest West Haven grade[1], *n* (%)	
1	6 (10)
2	20 (32)
3	24 (39)
4	12 (19)
Repeated HE-related hospitalizations (> 1), *n* (%)	42 (68)
Recurrent HE, *n* (%)	34 (55)

[1]The grade ranges from 0 to 4, with higher scores indicating more severe impairment. HE: Hepatic encephalopathy; TIPS: Transjugular intrahepatic portosystemic shunt; MELD: Model for end-stage liver disease.

Cessation of persistent HE

The probability of persistent HE cessation was 68%. The median time to disappearance was 78.3 d (95%CI: 52.0-104.7). After two months of treatment, more than 50% of patients concerned were free of persistent HE (Figure 3).

Bacterial infections and safety

Twenty-six patients had one or more bacterial infections during period 1 compared to 13 patients during period 2. The rate of infectious events per patient was similar before and after the introduction of rifaximin treatment (0.35 ± 0.47 *vs* 0.34 ± 0.54; P = 0.95). Rifaximin was well tolerated. Only 2 patients experienced adverse events leading to the discontinuation of the drug for one of them (pruritus and drug induced liver injury with no real correlation shown associated with the intake of rifaximin).

Predictive factors of response to treatment

All variables collected at the inclusion were analyzed and no significant difference was found. The main characteristics of both groups are summarized in Table 2.

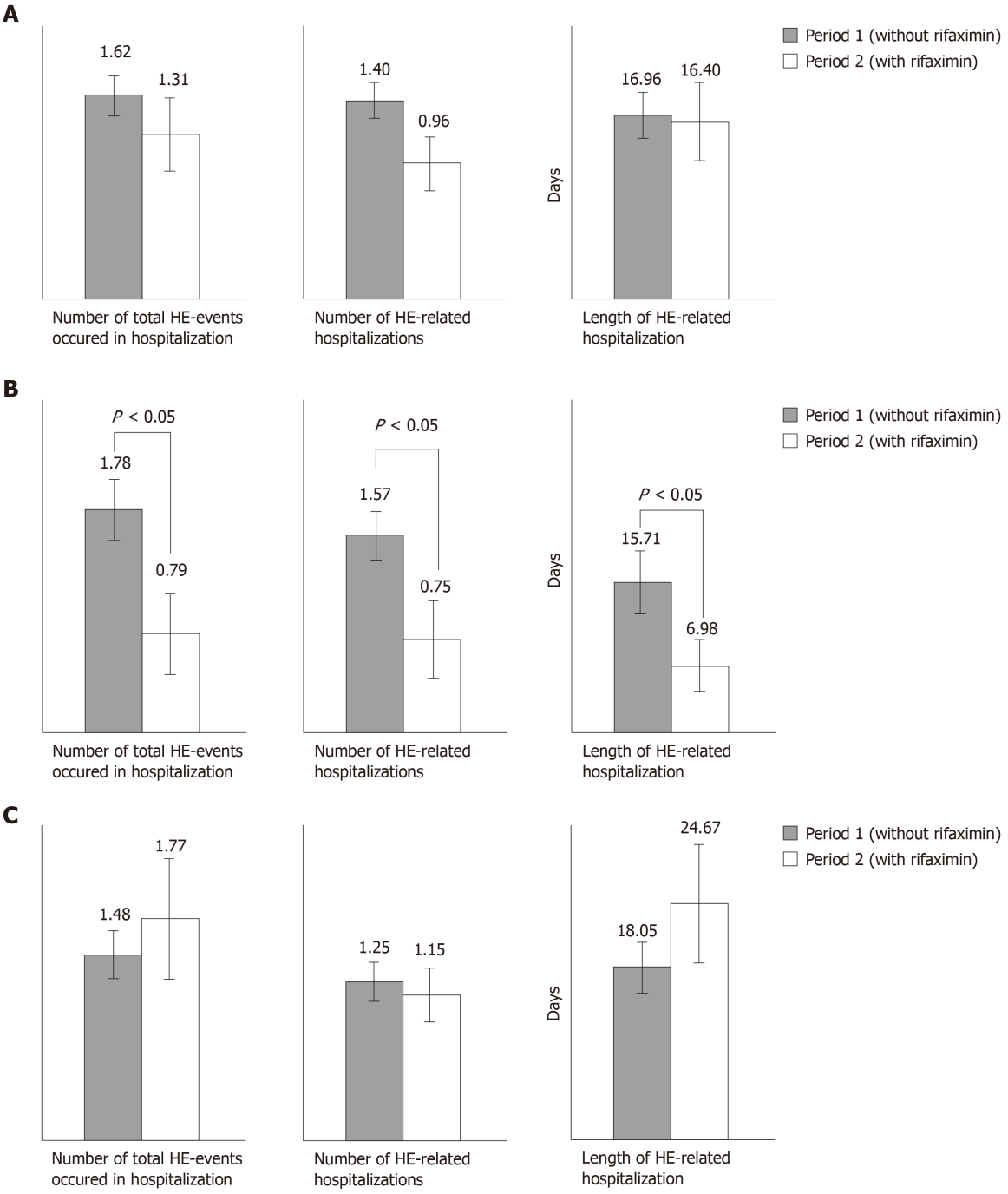

Figure 1 Comparison of hepatic encephalopathy events, hepatic encephalopathy-related hospitalizations and length of hepatic encephalopathy-related hospitalization with or without rifaximin for entire cohort and subgroups "prevention of recurrent hepatic encephalopathy" and "prevention of an acute episode on persistent hepatic encephalopathy". A: Entire cohort; B: Prevention of recurrent hepatic encephalopathy (HE) episodes; C: Prevention of recurrent acute exacerbations on persistent HE. The results are expressed for 100 d of follow-up. HE: Hepatic encephalopathy.

DISCUSSION

In this retrospective study conducted in two liver diseases centers, we found that rifaximin was efficient in secondary prevention in patients presenting recurrent episodes of HE by reducing the risk of HE recurrence associated with hospitalization. In fact, we observed a reduction of the total number of HE events, the number of HE-related hospitalizations, and the length of HE-related hospitalization by up to 50%. Conversely, we were not able to show any effectiveness of rifaximin in patients with recurrent acute exacerbations on persistent HE. We observed an upward trend in the number of HE events and in the duration of HE-related hospitalization as well as a downward trend in the number of HE-related hospitalizations. Likewise, a cessation of persistent HE in more than 50% of patients after two months of treatment has been observed. Nevertheless, this result does not take into account any subsequent

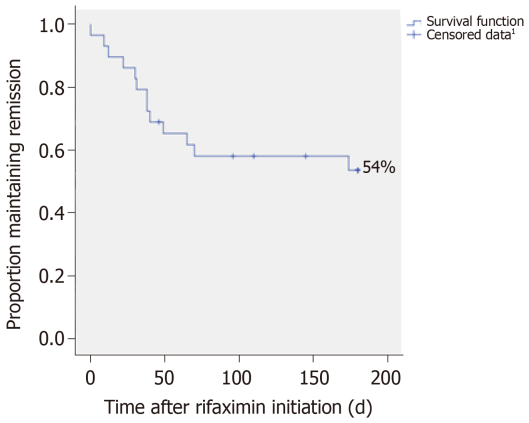

Figure 2 Probability of hepatic encephalopathy recurrence during rifaximin therapy in the subgroup "Prevention of recurrent hepatic encephalopathy", *n* = 29; Kaplan-Meier method.[1]Censored data correspond to discontinuation of treatment before the occurrence of hepatic encephalopathy (HE). At the end of follow-up, it corresponded to "HE-free" patients, after six months of treatment.

recurrences and does not ensure the maintenance of remission. Indeed, in this real-life study, rifaximin was efficient in patients receiving HE according to the manufacturer's recommendations.

Similarly, the PROSPER study which should enroll approximately 550 patients with HE, is ongoing under 'real world' clinical practice conditions. Results are still unavailable but the controlled design of this study could avoid some bias related to uncontrolled study[20]. Actually, it can be argued that in our study the sample size was relatively small, however we found results in accordance with the literature when rifaximin was used in patients with recurrent HE and without persistent HE[18]. The limited sample (n = 33) of patients suffering from recurrent acute exacerbations on persistent HE precludes any conclusions about the absence of rifaximin effectiveness in this subgroup of patients. Moreover, although not evaluated in our study, savings costs could be made due to a decrease in the number of rehospitalization. In the study of Orr *et al*[23], real world data from seven United Kingdom liver centers of patients with cirrhosis treated with rifaximin were analyzed (n = 326). Following the beginning of rifaximin treatment, the total hospital length of stay was reduced by between 31 and 53% resulting in an average saving of £4858-£6607 per patient per year in hospital admission costs.

Our results in the subgroup "prevention of recurrent HE episodes" are in accordance with those of Orr *et al*[23]. In this retrospective study, comparing the 6 mo pre-rifaximin and post-rifaximin initiation in living patients at the end of the observation period (n = 114), there were significant reductions in the average number of hospitalizations per patient (liver-related 1.3 to 0.5, $P < 0.001$), hospital bed days per patient (liver-related 17.8 to 6.8, $P < 0.001$), 30-day hospital re-admissions per patient (liver-related 0.5 to 0.2, $P = 0.039$) and emergency department attendances per patient (all-cause, 1.0 to 0.5, $P < 0.001$).

In our real life conditions, an off-label use of rifaximin was also found in more than half of the cases: the prevention of acute exacerbations in patients with persistent HE, *i.e.*, another form of recurrent HE. This use was associated with a lack of therapeutic alternatives and followed the failure of high-dose lactulose therapy. The literature data are relatively poor and unclear in the area of persistent HE; to our knowledge, an effectiveness assessment from this perspective is the first attempt. A few studies comparing rifaximin to nonabsorbable disaccharides demonstrated its efficacy in the management of HE events. However, baseline characteristics and the type of HE are not always clearly described. Most studies indicate an efficacy of rifaximin in the treatment of HE; some use the term "chronic" HE[24-31]. It can also refer to patients with recurrent episodes of HE as well as patients with continuous abnormalities of the mental state[32]. This underlines the difficulty to characterize HE and to appreciate its time course and its severity both in clinical practice as well as in clinical trials. Indeed, there is no standardized and reproducible tool to identify and grade HE[33]: The clinical examination can be based on different clinical scales, especially the West Haven criteria, the current gold standard[34]. However, this is a subjective and a non-standardized grading system with limited inter-observer reliability[4] which depends *e.g.*, on the clinician's own experience, the knowledge of the patient's previous condition and education and involvement of spouses or family members because many episodes or exacerbations of HE occur at home. Recently, Bajaj *et al*[33] therefore

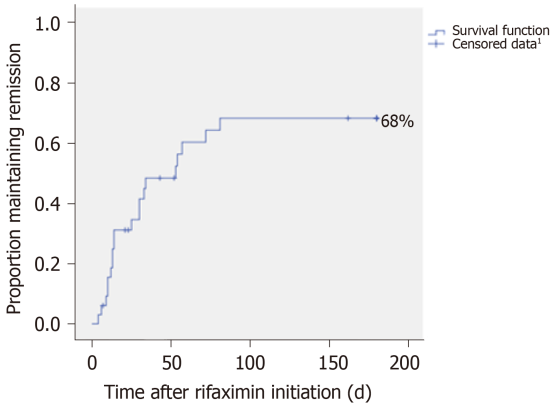

Figure 3 Cessation probability of persistent hepatic encephalopathy during rifaximin therapy in the subgroup "Prevention of an acute episode on persistent hepatic encephalopathy", *n* = 33; Kaplan-Meier method.[1]Censored data correspond to discontinuation of treatment before cessation of hepatic encephalopathy (HE). At the end of follow-up, it corresponded to patients with maintenance of persistent HE.

developed a standardized and reproducible clinical tool, the HE Grading Instrument, requiring further prospective applications[33]. The persistent form of HE makes us raise more questions, which are connected to a definition which is not specific enough: *e.g.*, how long does it take to consider an episode as persistent HE. The most recent proposed nomenclature of HE classifies the recurrent HE as a distinct entity; no details were provided concerning the acute exacerbations on persistent HE[4].

Considering the conflicting results in terms of effectiveness, some predictive factors of response have been researched. No significant results were obtained. It would probably have been more relevant to consider alcohol withdrawal and not the alcoholic etiology of cirrhosis as predictive factor because of the impact of alcohol on bacterial overgrowth and bacterial translocation involved in the pathogenesis of HE[35].

The main strengths of this study are: (1) The ability of the patients to serve as their own controls to overcome inter-individual variability and get results from small samples; and (2) The originality of its subject which is particularly interesting in the management of persistent HE. The main limitations of this study are acknowledged: (1) The small sample size especially in the subgroup of patients suffering from recurrent acute exacerbations on persistent HE precludes any conclusions about the absence of rifaximin effectiveness in this indication; (2) The effectiveness assessment is based on the most serious HE-events involving hospitalizations and does not take into account the outpatients events; (3) The data are based on non-standardized information obtained from hospitalization and consultation reports and depended on the evaluation of each clinician supporting cirrhotic patients; (4) The data from "TIPS patients" (*n* = 25; 40%) have not been analyzed as a separate entity. Because TIPS is a known risk factor of HE, the actual effectiveness of rifaximin on HE could have been underestimated[4]; and (5) The lack of a control group may limit the interpretation of the results. Numerous factors are involved in improving the patient's health status, including specific drug effect, placebo effect, other therapeutic measures introduced, and the natural history of the disease.

In conclusion, in this first "real life" experience, rifaximin was used for two indications in a similar way. In secondary prevention of recurrent episodes of HE, rifaximin prescription is validated by a consistent study and widely prescribed in this indication. For the prevention of acute exacerbations recurrence on persistent HE, this use is much more nebulous. After at least six months of therapy, the effectiveness of rifaximin was confirmed in preventing the recurrence of HE episodes; but we cannot conclude that rifaximin is effective in the management of persistent HE. However, we noticed some encouraging results with a certain probability of persistent HE cessation. Some randomized controlled trials are needed to assess the efficacy of rifaximin in this type of HE. Nevertheless, first of all, it seems necessary to develop standardized and reproducible tools to improve the patient' selection in clinical trials and allow results' comparisons among studies. It seems to be an essential step to achieve further progress in the management of HE in clinical practice.

Table 2 Predictive factors of response to treatment in the entire cohort (*n* = 62)

Parameter	Non-responder (*n* = 26)	Responder (*n* = 36)	*P* value
Indication, *n* (%)			
Prevention of recurrent HE episodes/prevention of recurrent acute exacerbations on persistent HE	13 (50)/13 (50)	16 (45)/20 (55)	0.66
Sex (M/F), *n* (%)	21 (81)/5 (19)	24 (67)/12 (33)	0.22
TIPS, *n* (%)	8 (31)	17 (47)	0.19
Cirrhosis etiology, *n* (%)			
Alcohol	20 (77)	21 (58)	0.13
Hepatitis-B or C virus	7 (27)	9 (25)	0.86
Lactulose therapy (period 1)			
Patients treated, *n* (%)	22 (85)	31 (86)	1.0
Mean dose, mean ± SD (g)	35 ± 17	39 ± 19	0.48
Age	63 ± 10	62 ± 10	0.89
HE (period 1)			
HE events, mean ± SD	1.41 ± 1.0	1.62 ± 1.16	0.23
HE-related hospitalizations, mean ± SD	1.3 ± 1.0	1.40 ± 0.95	0.16
Length of HE-related hospitalization, mean ± SD	14 ± 13	17 ± 16	0.51
Repeated HE-related hospitalizations (> 1), *n* (%)	16 (62)	26 (72)	0.37
Infectious events	0.31 ± 0.44	0.35 ± 0.47	0.92
Biochemical			
INR	1.7 ± 0.8	1.6 ± 0.4	0.71
Serum albumin (g/L)	28 ± 5	29 ± 5	0.63
Serum bilirubin (μmol/L)	63 ± 99	35 ± 20	0.11
Serum sodium (mmol/L)	134 ± 7	135 ± 5	0.62
Serum creatinine (μmol/L)	97 ± 50	107 ± 111	0.65
AST (UI/L)	59 ± 31	80 ± 135	0.45
ALT (UI/L)	33 ± 19	44 ± 30	0.11
Hemoglobin (g/dL)	10.4 ± 1.9	10.5 ± 1.7	0.79
CRP (mg/L)	13 ± 19	11 ± 11	0.67
Scores			
Child Pugh score	9 ± 2	9 ± 2	1.0
MELD score	16 ± 6	17 ± 6	0.53

HE: Hepatic encephalopathy; TIPS: Transjugular intrahepatic portosystemic shunt; INR: International normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein; MELD: Model for end-stage liver disease.

ARTICLE HIGHLIGHTS

Research background

Hepatic encephalopathy (HE) is a major complication of cirrhosis with independant prognostic significance. The clinical and economic burdens of HE is tremendous and growing worldwide. Therapies are needed to improve the quality of life of patients and to decrease the rate of hospitalizations and the economic consequences.

Research motivation

The current management of HE is mainly based on lactulose. Rifaximin has been shown to decrease the risk of HE recurrence in patients with episodic forms. HE can also be persistent. However, there is no drug support recommendation for rifaximin use in this setting.

Research objections

The study aimed at assessing the effectiveness of rifaximin in the management of recurrent episodes of HE and recurrent acute exacerbations on persistent HE, in "real life conditions".

Research methods

This is a retrospective study using a within-subjects design. The data of patients treated with rifaximin for HE is collected in two liver diseases centers, during the six-month period before and during the six-month period after the initiation of rifaximin. The primary effectiveness endpoint was the total number of HE events involving hospitalization.

Research results
In the case of patients presenting recurrent episodes of HE, we observed a significantly reduction of the total number of HE-events by up to 50%. Conversely, in the prevention of acute exacerbations in patients with persistent HE, an off-label use which has been found in more than half of the studied population, there was no significant difference in the number of HE-events.

Research conclusions
The effectiveness of rifaximin was confirmed in the prevention of HE episodes recurrence but was not proved in the prevention of acute exacerbations recurrence on persistent HE.

Research perspectives
We noticed some encouraging results with a certain probability of persistent HE cessation. Randomized controlled trials are needed to assess rifaximin efficacy in this type of HE. It seems necessary to develop standardized and reproducible tools to improve the patients' selection in clinical trials and allow results comparison among studies. It seems to be an essential step to achieve further progress in the management of HE in clinical practice.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Mrs Fanny Hadad for reviewing the English version.

REFERENCES

1 **Tsochatzis EA**, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014; **383**: 1749-1761 [PMID: 24480518 DOI: 10.1016/S0140-6736(14)60121-5]
2 **Zatoński WA**, Sulkowska U, Mańczuk M, Rehm J, Boffetta P, Lowenfels AB, La Vecchia C. Liver cirrhosis mortality in Europe, with special attention to Central and Eastern Europe. *Eur Addict Res* 2010; **16**: 193-201 [PMID: 20606444 DOI: 10.1159/000317248]
3 **Scaglione S**, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, Volk ML. The Epidemiology of Cirrhosis in the United States: A Population-based Study. *J Clin Gastroenterol* 2015; **49**: 690-696 [PMID: 25291348 DOI: 10.1097/MCG.0000000000000208]
4 **Vilstrup H**, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, Wong P. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014; **60**: 715-735 [PMID: 25042402 DOI: 10.1002/hep.27210]
5 **Moscucci F**, Nardelli S, Pentassuglio I, Pasquale C, Ridola L, Merli M, Riggio O. Previous overt hepatic encephalopathy rather than minimal hepatic encephalopathy impairs health-related quality of life in cirrhotic patients. *Liver Int* 2011; **31**: 1505-1510 [PMID: 22093325 DOI: 10.1111/j.1478-3231.2011.02598.x]
6 **Bajaj JS**, Schubert CM, Heuman DM, Wade JB, Gibson DP, Topaz A, Saeian K, Hafeezullah M, Bell DE, Sterling RK, Stravitz RT, Luketic V, White MB, Sanyal AJ. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. *Gastroenterology* 2010; **138**: 2332-2340 [PMID: 20178797 DOI: 10.1053/j.gastro.2010.02.015]
7 **Poordad FF**. Review article: the burden of hepatic encephalopathy. *Aliment Pharmacol Ther* 2007; **25** Suppl 1: 3-9 [PMID: 17295846 DOI: 10.1111/j.1746-6342.2006.03215.x]
8 **Neff G**, Zachry W III. Systematic Review of the Economic Burden of Overt Hepatic Encephalopathy and Pharmacoeconomic Impact of Rifaximin. *Pharmacoeconomics* 2018; **36**: 809-822 [PMID: 29651649 DOI: 10.1007/s40273-018-0641-6]
9 **Jepsen P**, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010; **51**: 1675-1682 [PMID: 20186844 DOI: 10.1002/hep.23500]
10 **Stewart CA**, Malinchoc M, Kim WR, Kamath PS. Hepatic encephalopathy as a predictor of survival in patients with end-stage liver disease. *Liver Transpl* 2007; **13**: 1366-1371 [PMID: 17520742 DOI: 10.1002/lt.21129]
11 **Bustamante J**, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, Rodés J. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol* 1999; **30**: 890-895 [PMID: 10365817 DOI: 10.1016/s0168-8278(99)80144-5]
12 **Fichet J**, Mercier E, Genée O, Garot D, Legras A, Dequin PF, Perrotin D. Prognosis and 1-year mortality of intensive care unit patients with severe hepatic encephalopathy. *J Crit Care* 2009; **24**: 364-370 [PMID: 19327960 DOI: 10.1016/j.jcrc.2009.01.008]
13 **Greenberg LH**, Momary H. Audiotoxicity and nephrotoxicity due to orally administered neomycin. *JAMA* 1965; **194**: 827-828 [PMID: 5898011 DOI: 10.1001/jama.1965.03090200135032]
14 **Smith TL**, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B, Tenover FC, Zervos MJ, Band JD, White E, Jarvis WR. Emergence of vancomycin resistance in Staphylococcus aureus. Glycopeptide-Intermediate Staphylococcus aureus Working Group. *N Engl J Med* 1999; **340**: 493-501 [PMID: 10021469 DOI: 10.1056/NEJM199902183400701]
15 **Vlachogiannakos J**, Saveriadis AS, Viazis N, Theodoropoulos I, Foudoulis K, Manolakopoulos S, Raptis S, Karamanolis DG. Intestinal decontamination improves liver haemodynamics in patients with alcohol-related decompensated cirrhosis. *Aliment Pharmacol Ther* 2009; **29**: 992-999 [PMID: 19210289 DOI: 10.1111/j.1365-2036.2009.03958.x]
16 **Abd-Elsalam S**, El-Kalla F, Elwan N, Badawi R, Hawash N, Soliman S, Soliman S, Elkhalawany W, ElSawaf MA, Elfert A. A Randomized Controlled Trial Comparing Nitazoxanide Plus Lactulose With Lactulose Alone in Treatment of Overt Hepatic Encephalopathy. *J Clin Gastroenterol* 2019; **53**: 226-230 [PMID: 29668561 DOI: 10.1097/MCG.0000000000001040]

17 **Elfert A**, Abo Ali L, Soliman S, Ibrahim S, Abd-Elsalam S. Randomized-controlled trial of rifaximin versus norfloxacin for secondary prophylaxis of spontaneous bacterial peritonitis. *Eur J Gastroenterol Hepatol* 2016; **28**: 1450-1454 [PMID: 27512927 DOI: 10.1097/MEG.0000000000000724]

18 **Bass NM**, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, Sigal S, Sheikh MY, Beavers K, Frederick T, Teperman L, Hillebrand D, Huang S, Merchant K, Shaw A, Bortey E, Forbes WP. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; **362**: 1071-1081 [PMID: 20335583 DOI: 10.1056/NEJMoa0907893]

19 **Sanyal A**, Younossi ZM, Bass NM, Mullen KD, Poordad F, Brown RS, Vemuru RP, Mazen Jamal M, Huang S, Merchant K, Bortey E, Forbes WP. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy - a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2011; **34**: 853-861 [PMID: 21848797 DOI: 10.1111/j.1365-2036.2011.04808.x]

20 **Krag A**, Schuchmann M, Sodatonou H, Pilot J, Whitehouse J, Strasser SI, Hudson M. Design of the Prospective Real-world Outcomes Study of hepatic encephalopathy Patients' Experience on Rifaximin-α (PROSPER): an observational study among 550 patients. *Hepatol Med Policy* 2018; **3**: 4 [PMID: 30288327 DOI: 10.1186/s41124-017-0029-9]

21 **Dharel N**, Bajaj JS. Definition and nomenclature of hepatic encephalopathy. *J Clin Exp Hepatol* 2015; **5**: S37-S41 [PMID: 26041955 DOI: 10.1016/j.jceh.2014.10.001]

22 **Swaminathan M**, Ellul MA, Cross TJ. Hepatic encephalopathy: current challenges and future prospects. *Hepat Med* 2018; **10**: 1-11 [PMID: 29606895 DOI: 10.2147/HMER.S118964]

23 **Orr JG**, Currie CJ, Berni E, Goel A, Moriarty KJ, Sinha A, Gordon F, Dethier A, Dillon JF, Clark K, Richardson P, Middleton P, Patel V, Shawcross D, Preedy H, Aspinall RJ, Hudson M. The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin-α. *Liver Int* 2016; **36**: 1295-1303 [PMID: 26950766 DOI: 10.1111/liv.13111]

24 **Loguercio C**, Federico A, De Girolamo V, Ferrieri A, Del Vecchio Blanco C. Cyclic treatment of chronic hepatic encephalopathy with rifaximin. Results of a double-blind clinical study. *Minerva Gastroenterol Dietol* 2003; **49**: 53-62 [PMID: 16481971 DOI: 10.1007/s12307-011-0068-5]

25 **Mas A**, Rodés J, Sunyer L, Rodrigo L, Planas R, Vargas V, Castells L, Rodríguez-Martínez D, Fernández-Rodríguez C, Coll I, Pardo A; Spanish Association for the Study of the Liver Hepatic Encephalopathy Cooperative Group. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blind, double-dummy, controlled clinical trial. *J Hepatol* 2003; **38**: 51-58 [PMID: 12480560 DOI: 10.1016/s0168-8278(02)00350-1]

26 **Paik YH**, Lee KS, Han KH, Song KH, Kim MH, Moon BS, Ahn SH, Lee SJ, Park HJ, Lee DK, Chon CY, Lee SI, Moon YM. Comparison of rifaximin and lactulose for the treatment of hepatic encephalopathy: a prospective randomized study. *Yonsei Med J* 2005; **46**: 399-407 [PMID: 15988813 DOI: 10.3349/ymj.2005.46.3.399]

27 **Leevy CB**, Phillips JA. Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy. *Dig Dis Sci* 2007; **52**: 737-741 [PMID: 17245628 DOI: 10.1007/s10620-006-9442-4]

28 **Jiang Q**, Jiang XH, Zheng MH, Jiang LM, Chen YP, Wang L. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. *Eur J Gastroenterol Hepatol* 2008; **20**: 1064-1070 [PMID: 19047837 DOI: 10.1097/MEG.0b013e328302f470]

29 **Eltawil KM**, Laryea M, Peltekian K, Molinari M. Rifaximin vs. conventional oral therapy for hepatic encephalopathy: a meta-analysis. *World J Gastroenterol* 2012; **18**: 767-777 [PMID: 22371636 DOI: 10.3748/wjg.v18.i8.767]

30 **Wu D**, Wu SM, Lu J, Zhou YQ, Xu L, Guo CY. Rifaximin versus Nonabsorbable Disaccharides for the Treatment of Hepatic Encephalopathy: A Meta-Analysis. *Gastroenterol Res Pract* 2013; **2013**: 236963 [PMID: 23653636 DOI: 10.1155/2013/236963]

31 **Sharma BC**, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol* 2013; **108**: 1458-1463 [PMID: 23877348 DOI: 10.1038/ajg.2013.219]

32 **Ferenci P**, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology* 2002; **35**: 716-721 [PMID: 11870389 DOI: 10.1053/jhep.2002.31250]

33 **Bajaj JS**, Frederick RT, Bass NM, Ghabril M, Coyne K, Margolis MK, Santoro M, Coakley DF, Mokhtarani M, Jurek M, Scharschmidt BF. Overt hepatic encephalopathy: development of a novel clinician reported outcome tool and electronic caregiver diary. *Metab Brain Dis* 2016; **31**: 1081-1093 [PMID: 27278222 DOI: 10.1007/s11011-016-9851-9]

34 **Ferenci P**. Hepatic encephalopathy. *Gastroenterol Rep (Oxf)* 2017; **5**: 138-147 [PMID: 28533911 DOI: 10.1093/gastro/gox013]

35 **Cesaro C**, Tiso A, Del Prete A, Cariello R, Tuccillo C, Cotticelli G, Del Vecchio Blanco C, Loguercio C. Gut microbiota and probiotics in chronic liver diseases. *Dig Liver Dis* 2011; **43**: 431-438 [PMID: 21163715 DOI: 10.1016/j.dld.2010.10.015]

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2020 January 27; 12(1): 21-33

DOI: 10.4254/wjh.v12.i1.21

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Observational Study

Imaging response predictors following drug eluting beads chemoembolization in the neoadjuvant liver transplant treatment of hepatocellular carcinoma

Francisco Leonardo Galastri, Felipe Nasser, Breno Boueri Affonso, Leonardo Guedes Moreira Valle, Bruno Calazans Odísio, Joaquim Mauricio Motta-Leal Filho, Paolo Rogério Salvalaggio, Rodrigo Gobbo Garcia, Márcio Dias de Almeida, Ronaldo Hueb Baroni, Nelson Wolosker

ORCID number: Francisco Leonardo Galastri (0000-0001-9599-3778); Felipe Nasser (0000-0002-3259-7142); Breno Boueri Affonso (0000-0002-2940-9016); Leonardo Guedes Moreira Valle (0000-0001-6255-340X); Bruno Calazans Odísio (0000-0002-1771-8233); Joaquim Mauricio Motta-Leal Filho (0000-0001-9844-6833); Paolo Rogério Salvalaggio (0000-0002-4109-2285); Rodrigo Gobbo Garcia (0000-0002-1968-9595); Márcio Dias de Almeida (0000-0003-4571-961X); Ronaldo Hueb Baroni (0000-0001-8762-0875); Nelson Wolosker (0000-0003-1991-3507).

Author contributions: Galastri FL designed the research study, performed procedures and wrote the paper; Nasser F, Affonso BB and Valle LGM contributed equally to this work, performed procedures and participated in the research; Odísio BC contributed to the project and review; Motta-Leal Filho JM and Salvalaggio PR contributed equally with research and statistical analysis; Garcia RG and Baroni RH contributed equally to radiological evaluation and analytical tools; de Almeida MD contributed to the clinical evaluation and follow-up of patients; Wolosker N contributed to the study project and writing of the paper.

Institutional review board

Francisco Leonardo Galastri, Felipe Nasser, Breno Boueri Affonso, Leonardo Guedes Moreira Valle, Rodrigo Gobbo Garcia, Department of Interventional Radiology, Hospital Israelita Albert Einstein, São Paulo 05652-000, Brazil

Bruno Calazans Odísio, Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX 77230, United States

Joaquim Mauricio Motta-Leal Filho, Radiology Department, Radiology Department, Heart Institute (InCor), University of São Paulo, São Paulo 05403-900, Brazil

Paolo Rogério Salvalaggio, Teaching and Research Institute, São Paulo, Brazil, Hospital Israelita Albert Einstein, São Paulo 05652-000, Brazil

Márcio Dias de Almeida, Department of Liver Transplant, Hospital Israelita Albert Einstein, São Paulo 05652-900, Brazil

Ronaldo Hueb Baroni, Department of Radiology, Hospital Israelita Albert Einstein, São Paulo 05652-000, Brazil

Nelson Wolosker, Department of Vascular Surgery, Hospital Israelita Albert Einstein, São Paulo 05652-000, Brazil

Corresponding author: Francisco Leonardo Galastri, MD, PhD, Staff Physician, Department of Interventional Radiology, Hospital Israelita Albert Einstein, Avenida Albert Einstein, 627, São Paulo 05652-000, Brazil. leogalastri@gmail.com

Abstract

BACKGROUND

Drug-eluting bead transarterial chemoembolization (DEB-TACE) is an endovascular treatment to release chemotherapeutic agents within a target lesion, minimizing systemic exposure and adverse effects to chemotherapeutics. Therefore, identifying which patient characteristics may predict imaging response to DEB-TACE can improve treatment results while selecting the best candidates. Predictors of the response after DEB-TACE still have not been fully elucidated. This is the first prospective study performed with standardized DEB-TACE technique that aim to identify predictors of radiological response, assessing patients clinical and laboratory characteristics, diagnostic imaging and

statement: This study was approved by the local institutional review board (CAAE 0199.0.028.000-11).

Informed consent statement: Written informed consent was obtained from all patients in this study.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

Manuscript source: Unsolicited manuscript

Received: July 12, 2019
Peer-review started: July 16, 2019
First decision: August 7, 2019
Revised: October 2, 2019
Accepted: December 6, 2019
Article in press: December 6, 2019
Published online: January 27, 2020

P-Reviewer: Akbulut S, Chiu KW, Govindarajan GK, Rubbini M
S-Editor: Ma YJ
L-Editor: A
E-Editor: Wu YXJ

intraprocedure data of the hepatocellular carcinoma treated in the neoadjuvant context for liver transplantation.

AIM
To identify pre- and intraoperative clinical and imaging predictors of the radiological response of drug-eluting bead transarterial chemoembolization (DEB-TACE) for the neoadjuvant treatment of hepatocellular carcinoma (HCC).

METHODS
This is prospective, cohort study, performed in a single transplant center, from 2011 to 2014. Consecutive patients with HCC considered for liver transplant who underwent DEB-TACE in the first session for downstaging or bridging purposes were recruited. Pre and post-chemoembolization imaging studies were performed by computed tomography or magnetic resonance. The radiological response of each individual HCC was evaluated by objective response using mRECIST and the percentage of necrosis.

RESULTS
Two hundred patients with 380 HCCs were examined. Analysis of the objective response (nodule-based analysis) demonstrated that HCC with pseudocapsules had a 2.01 times greater chance of being responders than those without pseudocapsules ($P = 0.01$), and the addition of every 1mg of chemoembolic agent increased the chance of therapeutic response in 4% ($P < 0.001$). Analysis of the percentage of necrosis through multiple linear regression revealed that the addition of each 1mg of the chemoembolic agent caused an average increase of 0.65% ($P < 0.001$) in necrosis in the treated lesion, whereas the hepatocellular carcinoma with pseudocapsules presented 18.27% ($P < 0.001$) increased necrosis compared to those without pseudocapsules.

CONCLUSION
The presence of a pseudocapsule and the addition of the amount of chemoembolic agent increases the chance of an objective response in hepatocellular carcinoma and increases the percentage of tumor necrosis following drug-eluting bead chemoembolization in the neoadjuvant treatment, prior to liver transplantation.

Key words: Hepatocellular carcinoma; Liver transplantation; Response evaluation criteria in solid tumors; Neoadjuvant therapy; Liver neoplasms

Core tip: This is the first prospective study performed with standardized drug-eluting bead transarterial chemoembolization technique that aim to identify predictors of radiological response, assessing patients clinical and laboratory characteristics, diagnostic imaging and intraprocedure data of the hepatocellular carcinoma treated in the neoadjuvant context for liver transplantation. Two hundred patients with 380 hepatocellular carcinomas were examined and we could conclude that the presence of a pseudocapsule and the addition of the amount of chemoembolic agent increases the chance of an objective response and increases the percentage of tumor necrosis in hepatocellular carcinoma following drug-eluting bead chemoembolization in the neoadjuvant treatment, prior to liver transplantation.

Citation: Galastri FL, Nasser F, Affonso BB, Valle LGM, Odísio BC, Motta-Leal Filho JM, Salvalaggio PR, Garcia RG, de Almeida MD, Baroni RH, Wolosker N. Imaging response predictors following drug eluting beads chemoembolization in the neoadjuvant liver transplant treatment of hepatocellular carcinoma. *World J Hepatol* 2020; 12(1): 21-33
URL: https://www.wjgnet.com/1948-5182/full/v12/i1/21.htm
DOI: https://dx.doi.org/10.4254/wjh.v12.i1.21

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, the seventh most frequent malignant neoplasm and it is the third leading cause of cancer-related death in the world[1-3]. Liver transplantation remains the best treatment option for patients whose HCC falls within the Milan criteria[4,5]. Nevertheless, insufficient organ donation demands priority criteria for transplantation in many countries[5]. To avoid HCC progression while on the waiting list, patients can receive neoadjuvant treatment if they are within the criteria "bridging therapy" or not "downstaging therapy", and remain eligible for transplantation[6,7]. In many centers, transarterial chemoembolization (TACE) is the treatment of choice for that purpose[8].

Although TACE has been proven effective for the treatment of intermediate stage HCC[4], tumor response as a neoadjuvant therapy prior to resection and liver transplantation, (BCLC stages 0, A and B) is less predictable[9]. Drug-eluting bead transarterial chemoembolization (DEB-TACE) is a novel endovascular treatment based on the use of microspheres that release chemotherapeutic agents within a target lesion, minimizing systemic exposure and adverse effects to chemotherapeutics[8-11]. Hence, identifying which patient characteristics may predict imaging response to DEB-TACE may improve treatment results when selecting the best candidates for neoadjuvant therapy.

Current publications regarding determinants of post-TACE tumor response seem to be based on published data using c-TACE, and on retrospective studies[12-14]. DEB-TACE's predictors of response have not been completely elucidated. This is the first single-center prospective study performed using a standardized DEB-TACE technique that aimed to identify predictors of radiological response, assessing patients clinical and laboratory characteristics, diagnostic imaging and intraprocedural data of HCCs treated in the neoadjuvant context for liver transplantation.

MATERIALS AND METHODS

This was a single-center, observational cohort, prospective study, conducted at the Interventional Medicine Center, and was approved by the local institutional review board (CAAE 0199.0.028.000-11). All patients signed an informed consent form.

Patients and eligibility

Two hundred consecutive HCC patients underwent DEB-TACE first session at our institution from April 1, 2011 until June 30, 2014, according to the outpatient treatment protocol[15]. These patients had a total of 380 tumors, and 323 of them were treated. Inclusion criteria was as it follows: patients with HCC BCLC staging 0, A or B, who took part in the liver transplantation program of the institution, in which the DEB-TACE procedure purpose was downstaging or for bridging strategy, and we assured they did not have extrahepatic spread or vascular invasion. Patient pre-treatment assessments was performed and included clinical and physical examination, imaging studies and laboratory tests — including contrast-enhanced magnetic resonance (MRI) or triple-phase computed tomography (CT). The intraoperative variables that were assessed were treatment-specific and general procedure data for each tumor. Exclusively the imaging results from the first session procedure were analyzed. The imaging was performed from 30 to 60 d after DEB-TACE and so the response evaluation.

DEB-TACE procedure

All procedures were performed under sedation (midazolam and fentanyl), intravenous analgesia and local an aesthesia with 2% lidocainee. Catheterizations were performed *via* common femoral artery, followed by superior mesenteric, celiac trunk and common hepatic artery angiograms performed with a Cobra 2 5F or Simmons 2 5F (Cordis, United States). With the angiograms, it was possible to outline the hepatic artery anatomy, to delineate the tumor and the vessels that supply it, and assess portal vein patency.

The feeding vessels previously identified were catheterized with a 2.8 F microcatheter (Progreat, Terumo, Japan), and followed by embolization of the tumors with injection of one vial of 100-300 μm DC-BEAD (Biocompatibles®, United Kingdom, LTDA) or 50-100 μm HepaSphere (Merit Medical Systems, United States) loaded with 50 mg doxorubicin mixed with iodinated contrast medium, in line with the manufacturers recommendations. Proximal embolization was defined by delivery of beads from the right or left hepatic artery; Segmental embolization by DEB-TACE delivery from segmental branches; and subsegmental embolization by the injection of beads from subsegmental or even more distal branches (Figure 1)[16].

When necessary to guide catheterization and evaluate tumor vascularization cone bean computed tomography (Xper CT, Philips, Netherlands) imaging was carried out.

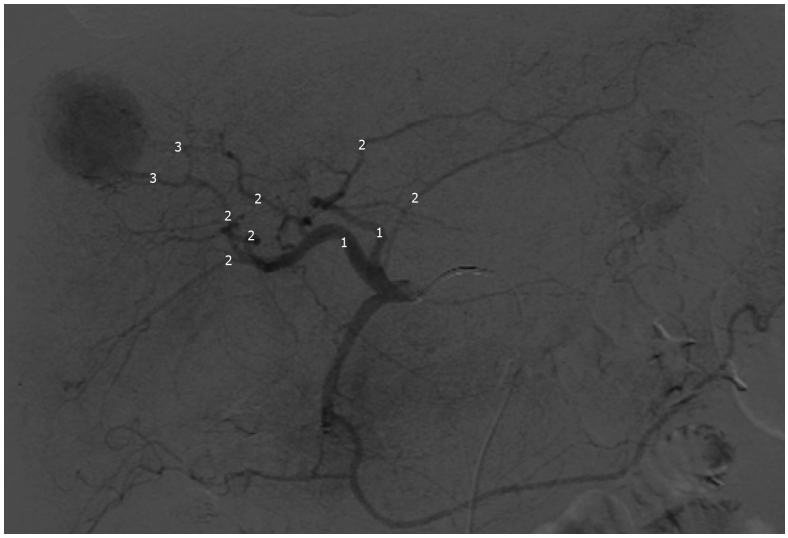

Figure 1 Hepatic angiography - arterial phase - and levels of superselection for administration of the chemoembolic agent. Superelelectivity levels for administration of the chemoembolic agent. 1: Proximal embolization: right/left hepatic artery trunk; 2: Segmental: right/left hepatic artery segmental branch; 3: Subsegmental branch of the right/left hepatic artery.

Whether the target lesion was hyper ou hypovascular, compared to the hepatic parenchyma in angiographic presentation, was also described (Figure 2). The endpoint was reached when near stasis was observed in the arterial branch(es) supplying the tumor. If that was no accomplished after the first procedure, the same HCC was identified in the database and later in another opportunity. The dose of chemoembolic agent used in each treated lesion was quantified. In situations such as proximal/contiguous lesion involvement, or where it was not possible to perform superselective catheterization and individualization of the target lesion, the following equation was used to individualize the dose of chemoembolic agent administered to the lesion (Figure 3). A suturing device (Perclose Proglide, Abbott, United States) was used for access closure in all patients.

Tumor response

The primary outcome of the study was to determine the radiological objective response (OR) of HCC to DEB-TACE therapy, as assessed by mRECIST guidelines[17,18]. The secondary endpoint of the study was to determine radiological response using the percentage of HCC necrosis after DEB-TACE therapy. Tumor response was evaluated in three manners.

Nodule-based analysis: Response of each treated tumor was evaluated and the baseline diameter prior to DEB-TACE was compared to the same tumor diameter after DEB-TACE, as stated by the mRECIST guidelines[17]. Complete response (CR) was defined as the absence of intratumoral contrast enhancement, and partial response (PR) when at least 30% decrease in diameter of the viable tumor was reached. Any case that did not meet for either partial response or progressive disease was considered as stable disease (SD), and progressive disease (PD) was defined as an increase of 20% or more in diameter of the viable tumor. OR was characterized as responder (RE) when the nodule reached CR and PR, and non-responder (NR) when the nodule reached SD and PD.

Target lesion response: The response of treated nodules was evaluated by comparing the baseline sum of diameters of target lesions previous to DEB-TACE with the sum of diameters of viable target lesions after DEB-TACE in each patient, according to mRECIST guidelines CR was defined as the absence of intratumoral contrast enhancement in all target lesions, and PR when at least 30% decrease in the sum of the diameters of the viable tumor was reached. Any case that did not meet for either partial response or progressive disease was considered as SD, and PD was defined as an increase of 20% or more in the sum of the diameters of the viable target lesions. OR was characterized as RE when the target lesion reached CR and PR, and NR when the target lesion reached SD and PD.

Individual response of treated HCC (% necrosis): Analysis of individual necrotic percentage response of each of the 298 treated HCCs was assessed by comparing the

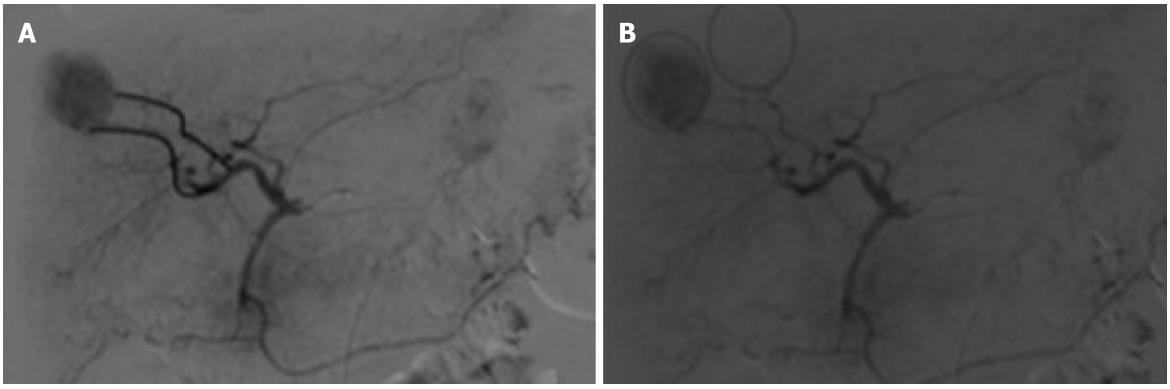

Figure 2 Representation of feeding vessels and hypervascularization of hepatocellular carcinoma in hepatic angiography. A: Hepatic angiography - arterial phase - showing, in solid line, projection two feeding vessels responsible for the formation of hepatocellular carcinoma who received chemoembolic agent dose; B: Hepatic angiography - arterial phase - showing the presence of a circular area in the projection of hepatocellular carcinoma with contrast medium concentration in relation to the adjacent area, being characterized as a hypervascular hepatocellular carcinoma.

largest axial diameter of necrosis of each tumor with the largest diameter of the same tumor post-DEB-TACE imaging.

Statistical analysis

Statistical analysis was performed using SPSS software, version 20.0 (IBM, Armonk, NY, United States). Differences between the means of continuous variables were compared according to the OR using Student's *t*-tests. Qualitative variables were described according to OR, and the association with chi-square test or exact tests (Fisher's exact test or likelihood ratio test) was verified. Pearson's correlations with quantitative variables were calculated for necrosis assessment and necrosis percentages were compared according to qualitative characteristics using Student's *t*-test or analysis of variance (ANOVA). To evaluate prognostic factors for OR, multivariate logistic regression analysis was performed and multiple linear regression analysis was used to evaluate prognostic factors of the percentage of tumor necrosis. For both models, the univariate analysis variables that were statistically significant for the outcomes were inserted, using the stepwise backward selection method with 5% input and output cryethium. The ROC (receiver operating characteristics) curve was constructed for the OR model to evaluate the quality of fit of the model. A p-value of less than or equal to 0.05 was considered significant.

RESULTS

In this study, 200 patients were included, with a total of 380 tumors detected at baseline imaging examinations. Of the 380 nodules, 323 were defined as target lesions and underwent DEB-TACE. The procedure was interrupted before embolization in one patient, with a single tumor, because he presented respiratory failure after sedation. Prior to the control imaging tests, 14 patients underwent hepatic transplant and were excluded. Therefore, the tumor radiological response was evaluated in 185 patients and the remaining 298 HCCs (Figure 4). The mean time between baseline CT/MRI and DEB-TACE was 40.2 d.

Target lesion response

According to OR for the target lesions (mRECIST; Target Lesion Response), no difference was observed between groups, concerning clinical characteristics, pre procedure laboratory and intraoperative information,as shown in Tables 1-3. Higher indirect bilirubin alone suggested a lower mean value in RE patients ($P = 0.05$) (Table 2).

Nodule-based tumor response

The individual preoperative radiological characteristics and intraoperative variables of HCCs were classified according to OR (mRECIST; nodule-based analysis). Upon univariate analysis, large HCC diameter ($P < 0.001$), the presence of a pseudocapsule ($P < 0.001$), increasing levels of chemoembolic agent delivered ($P < 0.001$) and larger numbers of feeding vessels ($P = 0.041$) were found to be predictive factors for OR (Table 4).

By multivariate logistic regression analysis, among variables that showed relevance

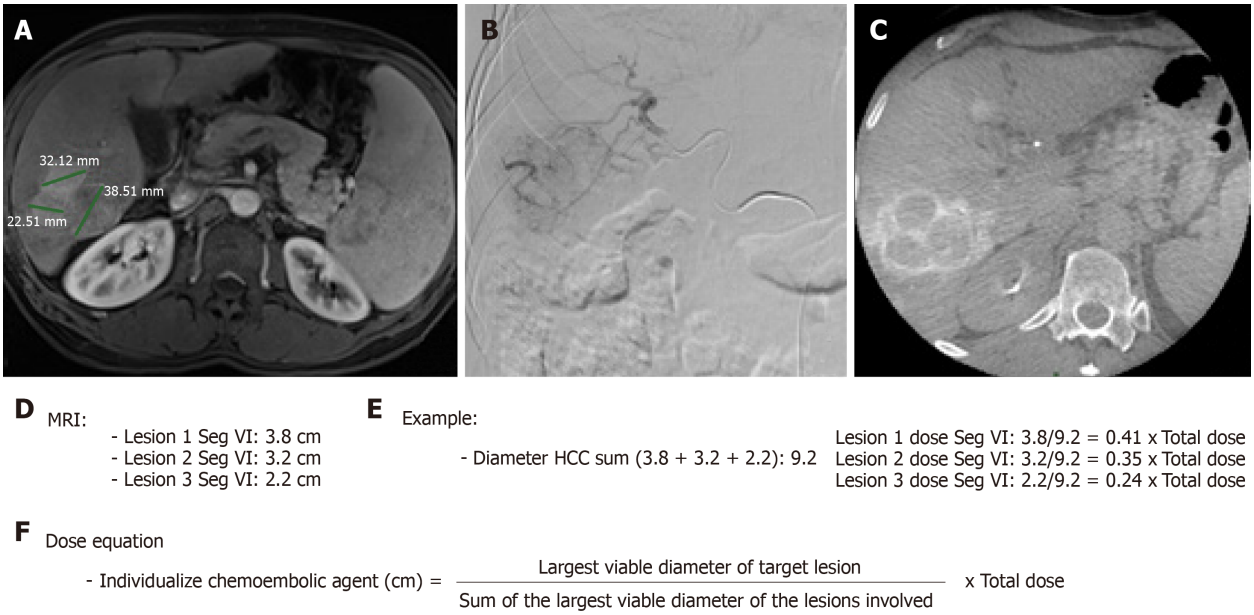

Figure 3 Calculation method for individualization of the dose of the chemoembolic agent received by treated hepatocellular carcinoma in situations of impossibility of the superselective catheterism. A: Magnetic resonance imaging pre-chemoembolization abdomen - post-contrast T1 weighted phase - showing three confluent hypervascular lesions; B: Selective hepatic arteriography in segment VI of the right hepatic artery showing hypervascular lesions characteristic of hepatocellular carcinoma; C: Intraoperative cone beam tomography with selective arterial contrast in segment VI - venous phase - showing three confluent lesions with contrast medium lavage; D: Diameter of hepatocellular carcinomas located in segment VI to be treated; E: Exemplification of the calculation of dose individualization of the chemoembolic agent administered; F: Equation of individualized chemoembolic dose. MRI: Magnetic resonance imaging.

alone, only the dose of the chemoembolic agent (OR = 1.04; 95%CI: 1.02-1.06, P < 0.001) and the presence of a pseudocapsule (OR = 2.01; 95%CI: 1.18-3.42) were jointly prognostic factors for OR (Table 5). For each milligram of chemoembolic agent solution administered, there was a 4% increase chance of the chemoembolized tumor being RE. The variables of number of feeding vessels and diameter of HCC lost statistical significance in the presence of the variables of the chemoembolic agent dose and pseudocapsule presence. Once a target tumor received the full dose of the 50 mg chemoembolic agent, it was 58.9% more likely to be RE than a tumor that received 1 mg chemoembolic agent. The chance of the tumor being RE when in the presence of a pseudocapsule was 2.01 times greater (95%CI: 1.18-3.42, P = 0.01) the chance of tumors without a pseudocapsule being RE (Table 5).

Despite the adjustments found for the dose of chemoembolic agent (mg) and pseudocapsule as explanatory variables for OR, the area under the curve (AUC) was 70.5% (Figure 5) indicating that other characteristics not evaluated in this study are also important additional factors that explain OR. Nevertheless, according to the ROC curve, these two variables presented an acceptable adjustment for OR.

Individual response of treated hepatocellular carcinoma (% necrosis)

When the necrosis rate was evaluated with respect to each of the tumor characteristics (Table 6), necrosis increased as HCC diameter increased (r = 0.210; P < 0.001) and as the dose of chemoembolic agent increased (r = 0.310, P < 0.001). The presence of a pseudocapsule conveyed, on average, a higher percentage of necrosis (P < 0.001). Regarding arterial catheterization, tumors chemoembolized through subsegmental branches presented a higher percentage of necrosis than tumors chemoembolized through segmental branches (P = 0.038).

However, according to multiple linear regression (Table 7), when evaluated together, only the dose of the chemoembolic agent and presence of a pseudocapsule were related to the percentage of necrosis. The addition of each 1 milligram of the chemoembolic agent resulted in an average increase of 0.65% in necrosis in the treated lesion, whereas HCCs with a pseudocapsule presented 18.27% more necrosis than CHCs without a pseudocapsule. On average, HCCs that did not receive mg of chemoembolic agent and did not have a pseudocapsule, presented 27.8% necrosis. This radiological response, as a percentage of HCC necrosis treated through the DEB-TACE, can be expressed by the equation:

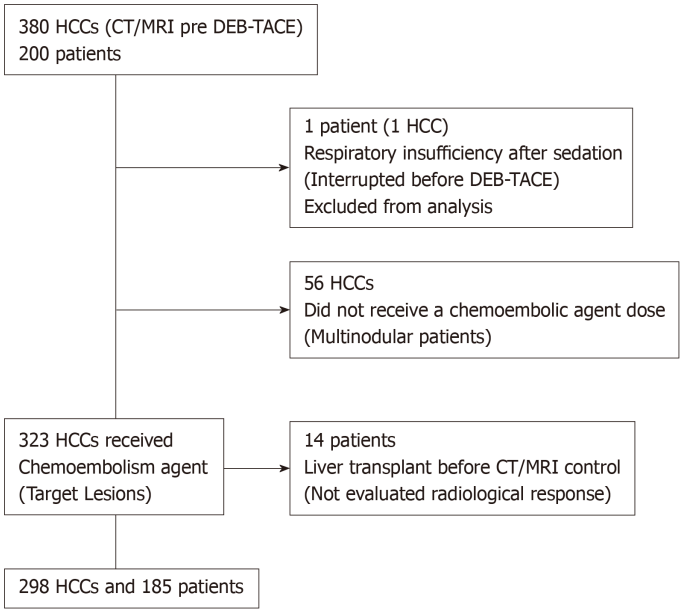

Figure 4 Flowchart of the patients included in the study. HCC: Hepatocellular carcinoma; CT: Computed tomography; MRI: Magnetic resonance imaging; DEB-TACE: Drug-eluting bead transarterial chemoembolization.

DISCUSSION

Radiological response to neoadjuvant HCC treatments is a fundamental method of evaluation for the decision to maintain and meet the criteria necessary for execution of a hepatic transplant[7,11]. Although the pseudocapsule was considered a predictor of radiological response in our study, this radiological characteristic of HCC cannot be differentiated from the true tumor capsule by imaging tests, requiring histopathological evaluation[19-21]. However, Ishigami *et al*[19] were able to correlate radiological findings of the pseudocapsule through histopathological analysis, evidencing that it was composed of prominent sinusoids and/or peritumoral fibrosis connecting to Glisson capsule fibrosis. Pseudocapsule HCCs, according to the same author, can be considered similar to those with a true fibrotic capsule histologically in terms of tumor invasiveness because the incidence of vascular invasion and degrees of cellular differentiation of evaluated tumors were similar[19].

In a previous study, evaluating 23 patients submitted to DEB-TACE in the same clinical stage of the current study who were submitted to liver transplantation, the presence of true capsule tumor was an independent predictor of histological response[22]. Similarly, studies evaluating changes in the histopathological architecture of HCCs treated with cTACE found that unencapsulated tumors have a worse response to cTACE than capped tumors, suggesting that unencapsulated lesions are primarily nourished by the portal vein[20]. Unlike our study, however, none of the cited studies were able to quantify the importance of the presence of pseudocapsules with respect to radiological response of HCC to DEB-TACE.

When we consider only those studies that used the DEB-TACE technique, we find Vesselle *et al*[23], a prospective cohort studying BCLC stage A and B patients[11,23], who were not candidates for curative therapy and used a heterogeneous caliber of embolic agent, identified that HCCs smaller than 5 cm were associated with a greater chance of CR and that tumors located in the hepatic segments I and IV presented worse radiological results[23]. In our study, the location of HCC in the hepatic segments, based on the hepatic segmentation of Couinaud, was not a predictor of radiological response (P = 0.961 OR, nodule-based analysis (mRECIST) and HCC treated P = 0.709, percentage of necrosis).

Odisio *et al*[22] evaluated histopathological response in a similar population with the same standardized DEB-TACE technique, dividing HCCs into two groups according to the diameter, 3.2 cm (95%CI: 2.55 -3.85) and 2.1 cm (95%CI: 1.79-2.48), and found a higher percentage of necrosis in HCCs with larger diameters. In our study, although the mean diameter of HCCs was related to radiological response, both according to OR of the individual HCC response, NR: 2.2 cm (SD: 1; 8.5 cm) and RE: 2.7 cm (P < 0.001), as well as the percentage of HCC necrosis treated (P < 0.001), when evaluated together with the dose of the chemoembolic agent and pseudocapsule, it did not retain statistical significance.

Table 1 Clinical characteristics according to objective response - target lesion response

Variable	NR (*n* = 44)	RE (*n* = 141)	Total (*n* = 185)	*P* value
Gender (male), *n* (%)	39 (88.6)	118 (83.7)	157 (84.9)	0.424
Age (yr), mean ± SD	58.7 ± 9.2	57.4 ± 8.1	57.7 ± 8.4	0.363[1]
BMI, mean ± SD	27.2 ± 4.2	27 ± 4.8	27.1 ± 4.7	0.717[1]
Systemic hypertension, *n* (%)	19 (43.2)	60 (42.6)	79 (42.7)	0.941
DM, *n* (%)	17 (38.6)	46 (32.6)	63 (34.1)	0.463
DLP, *n* (%)	1 (2.3)	9 (6.4)	10 (5.4)	0.456[2]
Smoker (%)	12 (27.3)	28 (19.9)	40 (21.6)	0.297
Coagulopathy[3, 4], *n* (%)	21 (47.7)	63 (44.7)	84 (45.4)	0.723
Thrombocitopenia[5], *n* (%)	28 (63.6)	93 (66)	121 (65.4)	0.778
CHILD, *n* (%)				0.705[6]
A	19 (45.2)	72 (52.6)	91 (50.8)	
B	20 (47.6)	56 (40.9)	76 (42.5)	
C	3 (7.1)	9 (6.6)	12 (6.7)	
MELD, mean ± SD	12.1 ± 3.5	11.9 ± 3.5	12 ± 3.5	0.605[1]
Downstaging[7] - Milan Criteria, *n* (%)	9 (20.5)	45 (31.9)	54 (29.2)	0.144
Multinodular HCC, *n* (%)	19 (43.2)	68 (48.2)	87 (47)	0.558

χ^2-test.
[1]Student's *t*-test;
[2]Fisher's exact test;
[3]Can't calculate;
[4]Patients with INR > 1.2[19];
[5]Patients with serum platelet counts < 150.000/mm^3[20];
[6]Probability ratio test;
[7]Patients undergoing neoadjuvant liver transplant treatment excluded from the Milan Criteria. NR: Non-responder; RE: Responder; BMI: Body mass index; DM: Diabetes mellitus; DLP: Dyslipidemia; CHILD: Child-Turcotte-Pugh classification; MELD: Model for end-stage liver disease; DEB-TACE: Drug-eluting beads transarterial chemoembolization; INR: International normalized ratio; HCC: Hepatocellular carcinoma.

There have been no published studies that related the dose of the chemotherapeutic agent used individually in each HCC in neoadjuvant DEB-TACE procedures with radiological response. In a study by Odisio *et al*[22], cumulative dose of the chemoembolic agent in all DEB-TACE sessions in which the HCC was submitted, was examined using histopathological results, and no statistical significance was observed. The elapsed time of more than one DEB-TACE procedure in addition to the waiting period for LT may have influenced the outcome of the histopathological evaluation. However, another factor that may justify the absence of this correlation in the study of Odisio *et al*[22], is the fact that the HCCs that did not reach vascular stasis until the end of the chemoembolic agent with carrier microspheres were administered the complementary embolization with microspheres (300-500 μm Bead Block, Biocompatibles, United Kingdom Ltd.) until reaching vascular stasis. In our study, the dose of the standardized chemoembolic solution of carrier microspheres was not supplemented with non-carrier microspheres, except in cases of tumor rupture, increasing the reliability of the method in reaching the same dose ratio in all HCCs of the chemoembolic/cm of viable HCC until vascular stasis is reached. HCCs that did not reach vascular stasis were identified and tested for radiological response as described in Tables 4 and 6. According to our study, the dose of chemoembolic agent administered individually in each HCC is directly related to radiological response when evaluated by the mRECIST OR method[18], as well as the percentage of necrosis.

Analysis of randomized univariate associations of demographic, laboratory, and comorbid data, according to Target Lesion Response (mRECIST)[17,18], showed that patients with OR showed lower values of indirect bilirubin (P = 0.05), indicating a possibility that the greater clinical severity of these patients may have influenced the worse performance of their radiological response. However, CHILD and MELD scores, specific scores for clinical liver function evaluation, were tested and were not statistically significance. Understanding the relationship of these severity criteria to DEB-TACE results in the neoadjuvant scenario to liver transplantation becomes important because the addition of neoadjuvant procedures to liver transplant brings with it an additional risk known for surgical procedures of patients staged in more advanced severity classes. Thus, the benefit of the use of DEB-TACE in this scenario should be evaluated in a rigorous and standardized way, to identify patients who can

Table 2 Pre procedure laboratory characteristics according to objective response - target lesion response (mRECIST)

Variable	NR (*n* = 44)	RE (*n* = 141)	Total (*n* = 185)	*P* value
Hb (g/dL)	12.9 ± 2.5	12.9 ± 2	12.9 ± 2.1	0.667[1]
Ht (%)	37.1 ± 6.7	37.4 ± 5.6	37.3 ± 5.9	0.862[1]
Creatinine (mg/dL)	0.95 ± 0.81	0.92 ± 0.86	0.93 ± 0.84	0.459[1]
Albumin (g/dL)	3.43 ± 0.53	3.34 ± 0.55	3.37 ± 0.54	0.575[1]
Alphafetoprotein (UI/mL)	200.3 ± 463	435.1 ± 2307.2	379.3 ± 2027.7	0.320[1]
Direct bilirubin (mg/dL)	0.73 ± 0.49	0.65 ± 0.41	0.67 ± 0.43	0.648[1]
Indirec bilirubina (mg/dL)	1.43 ± 0.87	1.14 ± 0.71	1.21 ± 0.76	0.050[1]
Total bilirubin (mg/dL)	1.9 ± 1.11	1.78 ± 0.89	1.81 ± 0.94	0.842[1]
INR	1.31 ± 0.19	1.31 ± 0.21	1.31 ± 0.2	0.778[1]
Platelets (x 10^3/mm^3)	85 ± 42.9	91.7 ± 54.8	90.1 ± 52.1	0.810[1]
AST (U/L)	87 ± 68.1	84.4 ± 59	85.1 ± 61.3	0.842[1]
ALT (U/L)	71.4 ± 52.4	71.5 ± 49.7	71.5 ± 50.2	0.825[1]

[1]Student's *t*-test. NR: Non-responder; RE: Respondent; Hb: Hemoglobin; Ht: Hematocrit; INR: International normalized ratio; AST: Glutamic-oxalacetic transamisnase; ALT: Glutamic-pyruvic transaminase.

obtain the maximum radiological response with the lowest clinical risk.

In relation to intraoperative variables [duration of the procedure (min), radioscopy time (min) and contrast volume (mL)] tested according to OR - Target Lesion Response (mRECIST) (Table 3), no statistical significance was observed with radiological response. Thus, possible assumptions were made that longer procedures, with a longer radioscopy time or requiring a greater volume of contrast medium during the DEB-TACE that were, therefore, more difficult, could present worse radiological results but were not confirmed.

Intraoperative variable for arterial catheterization, when evaluated by the percentage of HCC necrosis treated, suggested that tumors chemoembolized through subsegmental branches had a higher percentage of necrosis than tumors chemoembolized through segmental branches (P = 0.038). However, in a multiple linear regression analysis, this variable did not maintain statistical significance. Even when we evaluated the variable arterial selectivity according to OR - target lesion response (mRECIST), it was not statistically relevant. Thus, the perception that the best radiological response in transarterial procedures is obtained with the maximum superselecttion of the target HCC was not confirmed in this study.

The limitations of this study include that data analysis was related only to the first treatment of HCC by DEB-TACE, and there were some HCCs that did not achieve vascular stasis in this first session of DEB-TACE (not achieved the end point). Furthermore, use of the 50-100 μm Hepasphere carrier microsphere (Merit Medical Systems, United States) only occurred in 28 HCCs, while the 100-300 μm DC Beads, Biocompatible, United Kingdom Ltd. was used in the remaining 270 HCCs, so it was not possible to identify differences between these materials used in the radiological results.

Analysis of predictors of radiological response of DEB-TACE for the neoadjuvant treatment of HCC showed that a pseudocapsule increases the chance of HCCs being responders by 2.01 times, and every milligram of chemoembolic agent administered causes a 4% increase in the chance of HCC being responders. The addition of each 1 mg of the chemoembolic agent resulted in an average increase of 0.65% in necrosis, and the presence of a pseudocapsule causeds 18.27% more necrosis in treated HCCs.

Table 3 Intraoperative information according to objective response - target lesion response (mRECIST)

Variable	NR (*n* = 44)	RE (*n* = 141)	Total (*n* = 185)	*P* value
Duration (min)	60.9 ± 24.9	64.5 ± 24.8	63.6 ± 24.8	0.372[1]
Radioscopy time (min)	25.2 ± 11.7	25.2 ± 12	25.2 ± 11.9	0.927[1]
Contrast volume (mL)	251.8 ± 70.1	249.6 ± 63.1	250.1 ± 64.6	0.888[1]

[1]Student's *t*-test. NR: Non-responder; RE: Responder; Duration: Total time of chemoembolization procedure; Radioscopy time: Radioscopy time of the chemoembolization procedure.

Table 4 Characteristics of hepatocellular carcinoma according to objective response - nodule-based analysis (mRECIST)

Variable	NR (*n* = 93)	RE (*n* = 205)	Total (*n* = 298)	*P* value
Preoperative				
HCC diameter (cm)	2.2 (1; 8.5)	2.7 (1.1; 8)	2.5 (1; 8.5)	< 0.001[1]
Liver segment[2], *n* (%)				0.961[3]
1	2 (2.2)	4 (2)	6 (2)	
2	8 (8.6)	24 (11.7)	32 (10.7)	
3	5 (5.4)	15 (7.3)	20 (6.7)	
4	10 (10.8)	18 (8.8)	28 (9.4)	
5	9 (9.7)	23 (11.2)	32 (10.7)	
6	19 (20.4)	35 (17.1)	54 (18.1)	
7	23 (24.7)	46 (22.4)	69 (23.2)	
8	17 (18.3)	40 (19.5)	57 (19.1)	
Pseudocapsule, *n* (%)	47 (50.5)	149 (72.7)	196 (65.8)	< 0.001
Intraoperative				
Chemoembolic dosis (mg)	11.4 (1.5; 50)	22.5 (2.4; 100)	18.23 (1.5; 100)	< 0.001[1]
Feeding vessels				0.0411
mean ± SD	1.2 ± 0.4	1.3 ± 0.5	1.2 ± 0.5	
median (min; max)	1 (1; 3)	1 (1; 3)	1 (1; 3)	
Selective catheterization[@], *n* (%)				0.197[3]
Proximal	3 (3.4)	9 (5.2)	12 (4.6)	
Segmental	33 (37.9)	47 (27.2)	80 (30.8)	
Subsegmental	51 (58.6)	117 (67.6)	168 (64.6)	
Hypervascular[4], *n* (%)	70 (75.3)	156 (78.8)	226 (77.7)	0.502
End-point[5], *n* (%)	88 (94.6)	187 (91.2)	275 (92.3)	0.308

[1]Mann-Whitney test;
[2]Liver segmentation according to Couinaud;
[3]Likelihood ratio test;
[4]Hepatocellular carcinoma identified as hypervascular during hepatic angiography;
[5]Hepatocellular carcinoma that obtained vascular stasis during the first chemoembolization session. NR: Non-responder; RE: Responder; HCC: Hepatocellular carcinoma.

Table 5 Objective response – nodule-based analysis (mRECIST) – responder

Variable	OR	95%CI		*P* value
		Inferior	Superior	
Chemoembolic dose (mg)	1.04	1.02	1.06	< 0.001
Pseudocapsule	2.01	1.18	3.42	0.01

Multiple logistic regression.

Table 6 Characteristics of lesion according to percentage of necrosis - hepatocellular carcinoma treated

Variable	Description	*P* value
HCC diameter (cm)[1]	0.21	< 0.001
Chemoembolic dose (mg)[1]	0.31	< 0.001
Feeding vessel[1]	0.093	0.11
Liver segment[2]		0.709[3]
1	41.7 ± 49.2	
2	60.9 ± 43.6	
3	64 ± 38.9	
4	53 ± 42.4	
5	47.3 ± 42	
6	50 ± 43.6	
7	56.2 ± 41.3	
8	59.3 ± 43.2	
Pseudocapsule		< 0.001[4]
No	39.2 ± 43.8	
Yes	63.4 ± 39.2	
Selective catheterization[5]		0.038[3]
Proximal	70.4 ± 43.9	
Segmental	46.3 ± 41.6	
Subsegmental	59.1 ± 41.9	
Hypervascular[6]		0.988[3]
No	54.4 ± 43.6	
Yes	54.3 ± 42.2	
End point[7]		0.198[3]
No	66.1 ± 37.7	
Yes	54.2 ± 42.6	

[1]Pearson's correlation;
[2]Liver segmentation according to Couinaud;
[3]ANOVA;
[4]Student *t*-test;
[5]Selective catheterization levels for hepatic chemoembolization (Proximal: right/left hepatic artery trunk; Segmental: right/left hepatic artery segmental branch; Subsegmental: right/left hepatic artery subsegmental branch);
[6]Hepatocellular carcinoma identified as hypervascular during hepatic angiography;
[7]Hepatocellular carcinoma that obtained vascular stasis during the first chemoembolization session. Data expressed as mean ± SD. HCC: Hepatocellular carcinoma.

Table 7 Radiological response – % Necrosis – treated hepatocellular carcinoma

Variable	Coefficient	Standard-error	*t* value	*P* value
Constant	27.83	4.64	6	< 0.001
Chemoembolic dose (mg)	0.65	0.14	4.58	< 0.001
Pseudocapsule	18.27	5	3.66	< 0.001

Multiple linear regression.

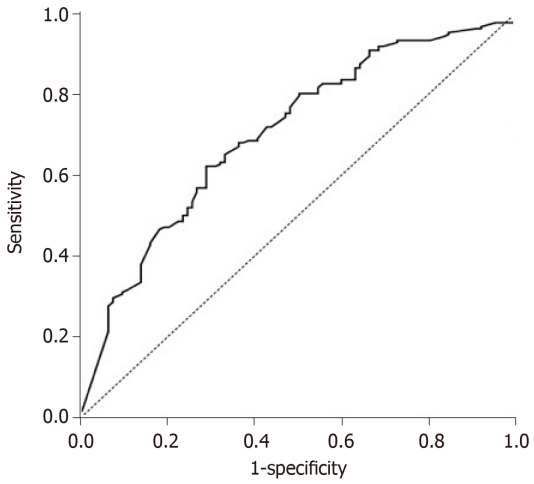

Figure 5 Receiver operating characteristics curve of prediction of hepatocellular carcinoma objective response.

Necrosis (%) = 27.8 + 0.65 (Dose of the chemoembolic agent) + 18.27 (Pseudocapsule[1])

[1]Pseudocapsule
- Absence = 0
- (Dose of the chemoembolic agent ≤ 50 mg)
- Presence = 1

ARTICLE HIGHLIGHTS

Research background
Drug-eluting bead transarterial chemoembolization (DEB-TACE) minimizes systemic exposure and adverse effects to chemotherapeutics in hepatocellular carcinoma (HCC) patients.

Research motivation
Predictors of the response after DEB-TACE still have not been fully elucidated.

Research objectives
Identifying characteristics which may predict imaging response can improve treatment results and select the best candidates.

Research methods
This was a single center, observational cohort prospective study.

Research results
Pseudocapsule increases by 2.01 times the chance of HCC to be responder and 18.27% more necrosis in treated HCCs. Every milligram of the chemoembolic agent administered causes a 4% increase the chance of HCC to be a responder and increase of 0.65% in necrosis.

Research conclusions
Pseudocapsule and the addition of the amount of chemoembolic agent are imaging response predictors following drug eluting beads chemoembolization in the neoadjuvant liver transplant treatment of hepatocellular carcinoma.

Research perspectives
Identify what other criteria not evaluated in this study may also be important additional factors explaining the post-DEB-TACE radiological response in the neodjuvant treatment of hepatocarcinoma.

REFERENCES

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
2 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]
3 **Raoul JL**, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, Lencioni R. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat Rev* 2011; **37**: 212-220 [PMID: 20724077 DOI:

10.1016/j.ctrv.2010.07.006]
4 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]
5 **Majno P**, Lencioni R, Mornex F, Girard N, Poon RT, Cherqui D. Is the treatment of hepatocellular carcinoma on the waiting list necessary? *Liver Transpl* 2011; **17** Suppl 2: S98-108 [PMID: 21954097 DOI: 10.1002/lt.22391]
6 **Frangakis C**, Geschwind JF, Kim D, Chen Y, Koteish A, Hong K, Liapi E, Georgiades CS. Chemoembolization decreases drop-off risk of hepatocellular carcinoma patients on the liver transplant list. *Cardiovasc Intervent Radiol* 2011; **34**: 1254-1261 [PMID: 21191590 DOI: 10.1007/s00270-010-0077-7]
7 **Graziadei IW**, Sandmueller H, Waldenberger P, Koenigsrainer A, Nachbaur K, Jaschke W, Margreiter R, Vogel W. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl* 2003; **9**: 557-563 [PMID: 12783395 DOI: 10.1053/jlts.2003.50106]
8 **Massarollo PC**, Coppini AZ, Salzedas-Netto AA, Coelho FF, Minami T, Gonzalez AM. Favorable Long-term Outcome in Patients Submitted to Liver Transplantation After Downstaging of Hepatocellular Carcinoma According to a Brazilian Selection Protocol. *Transplant Proc* 2016; **48**: 2338-2340 [PMID: 27742292 DOI: 10.1016/j.transproceed.2016.06.029]
9 **Abrams P**, Marsh JW. Current approach to hepatocellular carcinoma. *Surg Clin North Am* 2010; **90**: 803-816 [PMID: 20637949 DOI: 10.1016/j.suc.2010.04.010]
10 **Lencioni R**, Chen XP, Dagher L, Venook AP. Treatment of intermediate/advanced hepatocellular carcinoma in the clinic: how can outcomes be improved? *Oncologist* 2010; **15** Suppl 4: 42-52 [PMID: 21115580 DOI: 10.1634/theoncologist.2010-S4-42]
11 **European Association For The Study Of The Liver**. European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]
12 **Matsui O**, Kadoya M, Kameyama T, Yoshikawa J, Takashima T, Nakanuma Y, Unoura M, Kobayashi K, Izumi R, Ida M. Benign and malignant nodules in cirrhotic livers: distinction based on blood supply. *Radiology* 1991; **178**: 493-497 [PMID: 1846240 DOI: 10.1148/radiology.178.2.1846240]
13 **Yao FY**, Kerlan RK, Hirose R, Davern TJ, Bass NM, Feng S, Peters M, Terrault N, Freise CE, Ascher NL, Roberts JP. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology* 2008; **48**: 819-827 [PMID: 18688876 DOI: 10.1002/hep.22412]
14 **Angelico M**. TACE vs DEB-TACE: Who wins? *Dig Liver Dis* 2016; **48**: 796-797 [PMID: 27257050 DOI: 10.1016/j.dld.2016.05.009]
15 **Nasser F**, Cavalcante RN, Galastri FL, de Rezende MB, Felga GG, Travassos FB, De Fina B, Affonso BB. Safety and feasibility of same-day discharge of patients with hepatocellular carcinoma treated with transarterial chemoembolization with drug-eluting beads in a liver transplantation program. *J Vasc Interv Radiol* 2014; **25**: 1012-1017 [PMID: 24704346 DOI: 10.1016/j.jvir.2014.02.025]
16 **Cavalcante RN**, Nasser F, Motta-Leal-Filho JM, Affonso BB, Galastri FL, De Fina B, Garcia RG, Wolosker N. Occurrence of Vascular Lake Phenomenon as a Predictor of Improved Tumor Response in HCC Patients That Underwent DEB-TACE. *Cardiovasc Intervent Radiol* 2017; **40**: 1044-1051 [PMID: 28500458 DOI: 10.1007/s00270-017-1678-1]
17 **Lencioni R**, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30**: 52-60 [PMID: 20175033 DOI: 10.1055/s-0030-1247132]
18 **Gillmore R**, Stuart S, Kirkwood A, Hameeduddin A, Woodward N, Burroughs AK, Meyer T. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. *J Hepatol* 2011; **55**: 1309-1316 [PMID: 21703196 DOI: 10.1016/j.jhep.2011.03.007]
19 **Ishigami K**, Yoshimitsu K, Nishihara Y, Irie H, Asayama Y, Tajima T, Nishie A, Hirakawa M, Ushijima Y, Okamoto D, Taketomi A, Honda H. Hepatocellular carcinoma with a pseudocapsule on gadolinium-enhanced MR images: correlation with histopathologic findings. *Radiology* 2009; **250**: 435-443 [PMID: 19095782 DOI: 10.1148/radiol.2501071702]
20 **Higuchi T**, Kikuchi M, Okazaki M. Hepatocellular carcinoma after transcatheter hepatic arterial embolization. A histopathologic study of 84 resected cases. *Cancer* 1994; **73**: 2259-2267 [PMID: 7513245 DOI: 10.1002/1097-0142(19940501)73:9<2259::aid-cncr2820730905>3.0.co;2-p]
21 **Ishizaki M**, Ashida K, Higashi T, Nakatsukasa H, Kaneyoshi T, Fujiwara K, Nouso K, Kobayashi Y, Uemura M, Nakamura S, Tsuji T. The formation of capsule and septum in human hepatocellular carcinoma. *Virchows Arch* 2001; **438**: 574-580 [PMID: 11469689 DOI: 10.1007/s004280000391]
22 **Odisio BC**, Galastri F, Avritscher R, Afonso BB, Segatelli V, Felga GE, Salvalaggio PR, Ensor J, Wallace MJ, Nasser F. Hepatocellular carcinomas within the Milan criteria: predictors of histologic necrosis after drug-eluting beads transarterial chemoembolization. *Cardiovasc Intervent Radiol* 2014; **37**: 1018-1026 [PMID: 24149832 DOI: 10.1007/s00270-013-0759-z]
23 **Vesselle G**, Quirier-Leleu C, Velasco S, Charier F, Silvain C, Boucebci S, Ingrand P, Tasu JP. Predictive factors for complete response of chemoembolization with drug-eluting beads (DEB-TACE) for hepatocellular carcinoma. *Eur Radiol* 2016; **26**: 1640-1648 [PMID: 26455721 DOI: 10.1007/s00330-015-3982-y]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com