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Peritoneal carcinomatosis from advanced ovarian cancer: To treat or not to treat ethical issues suggested by a case study

Nacoti M *et al*. Treating the untreatable is somehow an option

Mirco Nacoti, Elena Colombetti, Maria Simonetta Spada, Marco Ceresoli, Luca Ansaloni, Gianmariano Marchesi, Luca Lorini, Davide Corbella, Federico Coccolini

Mirco Nacoti, Gianmariano Marchesi, Luca Lorini, Davide Corbella, Anesthesia and Intensive Care Department, Papa Giovanni XXIII Hospital, 24127 Bergamo, Italy

Elena Colombetti, Centre for Bioethics, Università Cattolica del Sacro Cuore di Milano, 20121 Milan, Italy

Maria Simonetta Spada, Clinical Psychology Unit, Papa Giovanni XXIII Hospital, 24127 Bergamo, Italy

Marco Ceresoli, Luca Ansaloni, Federico Coccolini, General Surgery Departement, Papa Giovanni XXIII Hospital, 24127 Bergamo, Italy

Author contributions: Nacoti M was the promoter of the bioethical conference and wrote the preliminary version of this manuscript; Colombetti E was the bioethical philosopher who conducted the conference, gave advice

upon the ethical issues raised by the case and revised the discussion; Spada MS performed the psychological evaluation and wrote all the part inherent the psychological profile; Ceresoli M, Ansaloni L and Coccolini F wrote the part of the manuscript inherent the surgical procedure and presented the update upon the indication of HIPEC in advanced ovarian cancer; Ceresoli M wrote the case presentation; Marchesi G and Lorini L were committed in organising the bioethical conference and took part in the revision of the discussion; Corbella D made the post-editing of the paper and revised the whole paper; all the authors red and approved the final manuscript.

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Correspondence to: Mirco Nacoti, MD, Anesthesia and Intensive Care Department, Papa Giovanni XXIII Hospital, Piazza OMS, 1, 24127 Bergamo, Italy. mnacoti@hpg23.it

Telephone: +39-35-2675110

Fax: +39-35-2674836

Received:

Peer-review started:

First decision:

Revised:

Accepted:

Abstract (no less than 200 words)

This article provides a brief description of an epithelial ovarian cancer (EOC) case (stage Ⅳ) treated with the association of complete CytoReductive Surgery and hypertermic intraPEritoneal chemotherapy (HIPEC). The use of HIPEC in EOC makes theoretic sense in view of the high rates of recurrence following standard treatment, but there are no randomized clinical trial to date and HIPEC for these patients still represents a radical treatment where the choice of no treatment may be acceptable since definitive cure is unlikely. We reviewed the entire decision making process considering the risk/benefit of the procedure in term of mortality/morbidity, the quality of life and the psychological profile of the patient 1 year after surgery. The platform World Health Organization-International Classification of Functioning, Disability and Health that permits evaluation of the person in relation to the psycho-social context is presented. A person-centred approach and assessment of health-related quality-of-life and disability in EOC survivors are of central importance for decision making.

Key words: Advanced epithelial ovarian cancer; Peritoneal carcinomatosis; Platform World Health Organization-International Classification of Functioning, Disability and health; Ethical issues; Hyperthemic intraperitoneal chemotherapy; Health related quality of life

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Nacoti M, Colombetti E, Spada MS, Ceresoli M, Ansaloni L, Marchesi G, Lorini L, Corbella D, Coccolini F. Peritoneal carcinomatosis from advanced ovarian cancer: To treat or not to treat ethical issues suggested by a case study. *World J Obstet Gynecol* 2015; In press

INTRODUCTION

The standard treatment for patients with advanced epithelial ovarian cancer (EOC) (stage Ⅲ or Ⅳ) is surgical debulking followed by platinum/paclitaxel-based adjuvant therapy. Although high rates of patients respond well to this therapy, about half of the patients relapse within 5 years[1] and long-term survival is achieved in only 10%-20% of patients[2]. Intraperitoneal route with the intravenous administration in primary stage Ⅲ ovarian cancer has been consequently studied in large randomized trials[3] and demonstrated that bidirectional chemotherapy using intravenous paclitaxel plus intraperitoneal cisplatin and paclitaxel significantly improved survival in patients with optimally debulked stage Ⅲ disease[4]. Despite these convincing data, intraperitoneal chemotherapy with normothermia still presents several limits, basically consisting of the inability of this technique to penetrate into tumor nodules larger than 3 mm[5].

On the other hand a significantly higher rates of treatment-related toxicities, side effects, complications[6-20] and a temporary reduction in quality of life[21-23] have been observed. All these adverse events could moreover lead to a potentially higher resource use[24,25]. To overcome these problems, intraperitoneal chemotherapy can be supplied intraoperatively, improving the tumor response to cancer chemotherapy drugs through the combination of drugs with hyperthermia[26,27]. Hyperthermia added to intraperitoneal

chemotherapy might enhance the antimitotic effect by several mechanisms as known since the second half of the 90s[28,29].

The association of complete cytoReductive surgery (CRS) and hypertermic intraperitoneal chemotherapy (HIPEC) has shown to improve survival in patients with pseudomyxoma peritonei, malignant peritoneal mesothelioma or peritoneal carcinosis from advanced abdomino-pelvic tumors with high level of evidence[30-33]. EOC has no definitive data upon the effectiveness of the association of CRS and HIPEC[34] but some ongoing randomized clinical trials are meant to assess the clinical efficacy of this therapeutic approach[35].

Two recently published systematic reviews, which analysed almost all the available international literature, concluded that this comprehensive treatment modality is a viable option in the management of patients with advanced EOC (stage III e IV disease), with potential benefits comparable with the current standard of care (conventional secondary cytoreduction or systemic chemotherapy)[3,4].

Practical implications at the basis of CRS and HIPEC has been presented on previously published studies focused on the quality of life (QoL) post procedure[23,24,36-40]. All of these studies, however, are limited by the fact that disability was not measured according to the conceptualization of disability endorsed by World Health Organization (WHO)'s International Classification of Functioning, Disability, and Health (ICF)[41] which defines disability as the relationship between one's health condition and environmental factors expressed in activity limitations and/or participation restrictions.

No article was found regarding the use of an ethical advice for decision making in case of advanced EOC. Few physicians sought external ethical advice and decisions were entirely taken by the medical team. Direct involvement of family and treating physician was limited[42]. The main goal of this paper is to offer ethical consideration useful for decision making for advanced EOC, when HIPEC represents a radical treatment for patients where the choice of no treatment may be acceptable since definitive cure is unlikely.

RESEARCH

In this article we presented one case of advanced EOC (stage Ⅳ) treated with CRS and HIPEC with favourable outcome (grade 1) in term of Common Terminology Criteria for Adverse Events (CTAE)[43] classification after 1 year of follow-up. The patient gave written informed consent to this case presentation.

We discussed the case after 1 year with the main specialists involved in the care process: surgeon, oncologist, anaesthetist and intensivist.

We reviewed the entire decision making process taking into consideration the risk/benefit of the procedure in term of mortality/morbidity, quality of life and psychological profile of the patient 1 year after surgery.

A clinical psychologist and a bioethicist philosopher took part at the discussion.

CASE PRESENTATION

Clinical picture

The patient was a 64-year-old woman. Twenty-seven years ago she had a breast cancer, initially treated with quadrantectomy and chemotherapy and after a relapse treated with mastectomy and chemotherapy in 2001; consecutive follow-ups were negative.

In December 2011, an advanced EOC (FIGO stage Ⅳ) was diagnosed. She underwent total body computed tomography-scan that showed a pelvic mass with massive ascites and pleural effusion positive for tumor cells. The diagnosis of an EOC serous type was made by transvaginal biopsy. Markers were elevated (CA125: 500 U/mL). She had 6 cycles of neoadjuvant chemotherapy with carboplatin (CDDP) and paclitaxel (PTX) with partial clinical response according with Response Evaluation Criteria In Solid Tumors criteria: the CA125 concentration was significantly diminished (75 U/mL); positron emission tomography scan was negative.

In June 2012, a month since chemotherapy, the patient underwent cytoreductive surgery with HIPEC: the Peritoneal Cancer -Index score was 5

and at the end of surgery no macroscopic residual disease was detected (Completeness of Cytoreduction 0[29]). She was discharged after 19 d: during the hospital stay she developed a severe thrombocytopenia (platelets < 20000). After two months from the surgery she underwent 3 cycles of adjuvant chemotherapy with CDDP and PTX. At the bioethical conference (12 mo since surgery) she was alive with no evidence of relapse.

Decision making: A surgical point of view

When the patient received the communication of the advanced EOC, she lived the diagnosis as a sentence that triggers the sense of the end.

Patient simplified a lot her condition. The main question was: "How much time remains and will Ⅰ suffer from it?" She asked for a longer life and does not ask for quality of life. Surgeon spoke with her clearly. "Advanced EOC lead the patient to die with bowel occlusion without treatment. CRS and HIPEC allows a five years cancer-free in 15%-20% of the patients". He proposed this option as an experimental treatment conducted in a clinical trial. Patient and her family had two weeks to decide what to do. The crucial problem was the level of invasive treatment proposed. This consultation has the difficulty to balance the incidence of EOC recurrence and postoperative complications of CRS and HIPEC against the optimal front-line chemotherapy including a combination of platinum analogue and taxane.

Psychological profile one year after procedure

The patient accessed the interview willingly. Lucid and oriented over space and time, reality testing was intact. Attention, memory and concentration appeared to be adequate. Psychopathology history was negative. She constructs her history anchoring the events of illness that saw her, a 39-year-old woman with two young daughters, dealing with the cancer disease.

Her narration shows the presence of a lively temperament and determined character. When the disease and other tragic events, such as the

loss of their first child at the end of pregnancy, have taken place in her life, she dealt with confidence in the doctors and her resources, but, at the same time, aware of the risks present.

She describes her husband as a person of few words, but with which she has a solid relationship characterised by the sharing of everyday life. Even the daughters, both married and with children, along with extended families, are a significant landmark and, even in the event of illness, were present and supportive.

When she dwells on the surgical procedure repeats several times: "if I had known that this recovery would have been so hard..." but then she concludes, "but my daughter says that I would have done the same".

In particular, she recalls the fear experienced in the post-intervention linked to the perception of a body that did not respond to commands and a shooting time that it seemed very long. Scar tissue are frequently emphasised in her speeches to husband that minimizes, and through some ironic joke, contributes to the acceptance the lady is building towards a change in her body.

She complains a strong weakness on the afternoon during which she stays in a chair for a long time. On the morning she perceives herself, in continuity with her whole life, as active and energetic; on the afternoon she seats throughout the rest of the day in an armchair because of fatigue. This situation forces her to a lifestyle in which she does not recognize. People do not always understand this fatigue, but the spur of the others makes her nervous.

ETHICAL CONSIDERATIONS

CRS is associated with morbidity and mortality and it is difficult to determine whether mortality and morbidity occurring after major CRS and HIPEC is caused by the surgery or the HIPEC or by the natural history of the EOC disease. Chua *et al*[4] reviewed 19 studies including CRS and HIPEC and found mortalities between 0% and 10% from any cause within 30 d of surgery. Postoperative events are common but mostly grade I (self-limiting) or grade Ⅱ,

requiring only medical treatment for resolution[35]. Grade 1 events occurred in 22 of 30 (73%), including transient nausea and vomiting, diarrhea, thrombocytopenia, and pleural effusion. One or more grade 2 events occurred in 27 patients (90%), including nausea and vomiting, cardiac arrhythmia, hypertension, diarrhea, pleural effusion, line sepsis, and increased creatinine. Twelve patients (40%) experienced 1 or more grade ⅢIcomplications that required invasive intervention, including anemia, pleural effusion, pneumothorax, fascial dehiscence, diarrhea, ileus, and pancreatic leakage.

The use of HIPEC in EOC is aimed at reduction of the high rates of recurrence following standard treatment. CRS and HIPEC allows a five years cancer-free in 15%-20% of the patients with EOC. Experience reported in the literature is increasing, but there are no randomized clinical trial to date[34] and HIPEC still represents a radical treatment for patients where the choice of no treatment may be acceptable since definitive cure is unlikely.

For this reason HIPEC in EOC should ideally be performed on a research protocol or their data prospectively collected in registries such as the Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer registry[35]. Every study should always be functional to the patient. It's important to ensure that the patient does not become subordinate to a research protocol because the feasibility of a treatment does not exhaust the question. Medical code of ethics states "Every treatments that affect the integrity and the mental and physical strength of the patient may be implemented, following an assessment of care needs, and only in order to obtain a real clinical benefit to the patient or alleviate their suffering. The doctor, also taking into account the patient's wishes if expressed, must refrain in diagnostic and therapeutic treatments from which we can't reasonably expect a benefit to the health of the patient and/or an improvement in quality of life"[44].

Even if the case presented had a good outcome (grade Ⅰ as defined by CTAE classification), the patient has a strong weakness one year after CRS and HIPEC that forces her to a lifestyle in which she does not recognize herself. She

says “if I had known that this recovery would have been so hard...” In this complex situation the bioethical question is crucial.

Bioethics should be meant as the critical conscience of technological civilization that moves philosophical questions on the significance of the construction of human identity within the technological action. In this context the need to think of the technological process, involves the whole person and belongs to each person[45]. This “critical” enterprise should be participated by all those who, from different perspectives and with different cultural backgrounds, are interested in understanding the historical condition of contemporary human being. The field of bioethics is not derived solely from the fact that what is being discussed is theoretically and practically complex, but for the reason that the truth is an ethical judgment from the empirical data of other sciences. Bioethics loses its specificity if it does not examine the historical condition in which it addressed the question of life today: the binomial life-ethics placed inside the filter with which the experimental sciences think and govern the phenomena of life[45].

For this reasons the ethical data can never be an element that arises at the end of a process. We can’t move the ethical question only when the evidence based medicine is uncompleted, as in EOC, because the wellness of the patient is not a clinical judgment. The ethical aspect can never be separated from the clinical practice because every human act has an ethical value and its lawfulness does not end in an appropriate technical gesture. It’s necessary to make explicit the anthropological aspect that influences clinical decisions.

A help to the analysis of the situation of the patient can came from the platform World Health Organization- International Classification of Functioning, Disability and Health (WHO-ICF), that permits evaluation of the person in relation to the psycho-social context[41]; it also should help researchers and clinicians to reinterpret terminology or expressions they use daily, such as quality-of-life, proportionality, informed consent, rights, autonomy, vulnerability, discrimination, participation, from the perspective of ethics[46].

The ICF introduces a new conceptual and operational model that promotes a new vision of health and disability, and it is based on the definition of disability as a ''difficulty in functioning at the body, person, or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors''[47]. Usually, physicians hypothesize the existence of a strict relationship between the patient's health related quality of life (HRQoL) and disability: the higher the disability is, the more impaired the HRQoL. All of these studies, however, are limited by the fact that disability was not measured according to the conceptualization of disability endorsed by WHO's ICF[41,48]. Therefore, changes in HRQoL or in disability profiles are again only explained by changes in a person's intrinsic health state. Patients reporting worse health status also reported higher levels of disability and lower quality-of-life. This finding shows that not only an objective, namely medically assessed, health status is related to quality-of-life and disability, but also health status perceived by patients is an important aspect to understand quality-of-life and disability[49]. A person-centered approach and assessment of health-related quality-of-life and disability in EOC survivors are of central importance. In fact, persons who experienced CRS and HIPEC, including those who are not severely affected anymore, report a substantial impact of the disease on some areas of participation[22,23,36-40]. For this reason, the identification of participation areas that are mostly affected by the disease can provide useful inputs to guide rehabilitation and care. For example, younger people not only have different rehabilitation needs and personal resources compared with older persons but also encounter different opportunities in tackling daily life difficulties in their workplace, community, and other settings. They experience the environment in different ways. In this sense, seeing the person in the interaction with the environment might explain why self-reported levels of health, disability, and HRQoL change among persons. Exploring the HRQoL in term of ICF's concept allows to evaluate the person in relation to the psycho-social context and to define the proportionality of the treatment. There

is a strictly clinical judgment on the proportionality which defines the cost-benefit of the treatment, but also the patient point of view determines the proportionality. The tolerability of the condition takes part in the determination of proportionality, which has not to be confused with the expectations of the patient. Tolerability must be evaluated in term of pain but also in term of feeling of suffering. Treatment planning with the patient helps to assess the tolerability. The evaluation of feasibility of CRS and HIPEC considering the concept ICF "of disability and functioning" can help both doctor and patient to decide not only in term of survival, but also in term of HRQoL. The final decision must come from a doctor-patient negotiations (and not from a contractual process), in which the doctor has to be aware that the decision making is never equal.

The informed consent stays at the end of this communication process and requires enough time to create an adequate relational context. The patient's informed decision not exhaust the relationship, but still remains a working progress where the patient should have the chance to change his decision, because the psico-social context may change.

Some data suggest that when patients fully understand their situation as a "terminal state" they are less likely to submit to extensive, life-threatening or QoL-threatening therapies[50,51].

It is likely that any treatment will impair QoL, at least in the short-term. However, like health, quality-of-life as well is the result of the interaction of many elements. Consequently, both the attribution of a complete subjective meaning to this concept and its transformation into a mere quantitative parameter should be avoided[46]. On the one hand, emphasizing the concept of the quality-of-life by drawing on people's subjective experience (desires, expectations, projects, *etc.*) involves the loss of the intersubjective perspective, which establishes the relationship between rights and duties. On the other hand, focusing on the quantitative parameters, that are more easily measured, may determine misunderstandings in the assessment of the relevance of the

quality-of-life for the individual. All of that implies a new idea of well-being: the quality of life also derives from the quality of relationships[46].

The aim of the article was not to suggest an interventional protocol to guide the decision, but an EOC patient-centered ethical approach through the platform WHO-ICF that permits evaluation of the patient in relation to the psycho-social context. This approach may improve the decision making process of both patient and doctor without removing individual responsibility.

CONCLUSION

The need to raise the subject of disability as a relationship between environment and pathological condition derives from a single fact: the changes in the living conditions in Western societies resulting from scientific and technological progress made it possible for an ever increasing number of people to live with their disease, with their impairments. The recognition of this fact is useful in addressing, not only issues related to the disease (which can be only partially addressed), but also for environmental intervention planning and it is therefore crucial to think of the treatment relationship as a question of justice[52].

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P-Reviewer: S-Editor: L-Editor: E-Editor: