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Treatment of diffuse malignant peritoneal mesothelioma (DMPM) by cytoreductive surgery and HIPEC

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Aim. Diffuse malignant peritoneal mesothelioma (DMPM) is a rare and locally aggressive tumor with poor prognosis, related in most cases to asbestos exposure. It is increasing in frequency, but currently no standard therapy is available. The biology of this disease is still poorly understood. Several highly specialized centers have recently reported improved survival by means of an innovative local-regional approach. The purpose of this article is to evaluate the survival benefit and the morbidity rate of patients affected by DMPM treated at our institution by cytoreductive surgery (CRS) associated with hyperthermic intraperitoneal perioperative chemotherapy (HIPEC).

Methods. This study includes 42 patients affected by DMPM treated by an uniform approach consisting of cytoreductive surgery associated with HIPEC using cisplatin and doxorubicin. The primary end point was overall survival and morbidity rate. The secondary end point was evaluation of prognostic variables for overall survival.

Results. The median follow-up period was 72 months (range 1-235 months). Thirty-five patients (83.3%) presented epithelial tumors and 7 were affected by multicystic mesothelioma. The mean peritoneal cancer index (PCI) was 13. Thirty-eight patients (90.4%) had complete cytoreduction (CC-0/1). The overall morbidity rate was 35.7% associated to a perioperative mortality of 7.1%. Median overall survival rate was 65 months with a 1- and 5-year survival rates of 63% and 44%, respectively.

Conclusion. The treatment of DMPM by CRS+HIPEC in selected patients is a feasible technique that allows to achieve encouraging results in terms of overall survival rate, with an acceptable morbidity rate. Further investigations are needed to clarify the role and the timing of this promising technique.

Key words: Mesothelioma - Asbestos - Carcinoma - Fever.

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare disease (related in most cases to asbestos exposure), but increasing in frequency. The incidence is approximately one per 1,000,000. Because of its unusual nature, the disease has not been clearly defined either in terms of its natural history, diagnosis or management. It represents about one fifth to one third of all forms of mesothelioma. Asbestos exposure appears to be causative in some cases of peritoneal mesothelioma, but a search for other carcinogens continues.

Patients affected by DMPM generally present with abdominal pain, tumor mass or nodules, often associated to ascites and
abdominal distention. Peritoneal mesothelioma is usually a rapidly fatal peritoneal surface malignancy with a median survival of less than 1 year.²

Few therapeutic advances have occurred in the last century, since the disease was first described by Miller and Wynn⁷ in 1908. Systemic chemotherapy, palliative surgery and/or total abdominal radiation therapy have been used selectively but have failed to alter the natural history of this disease.², ³, ⁸–¹² Over the past decade, the management of these patients has evolved similarly to ovarian cancer treatment and now it involves cytoreductive surgery (CRS) associated to hyperthermic perioperative intraperitoneal chemotherapy (HIPEC) with cisplatin and doxorubicin. This new treatment strategy has shown favorable prognosis and has achieved a median survival of up to 60 months and a 5-year survival of 50% in selected patients.¹³ Even if modern systemic chemotherapy based on cisplatin and peremetrexed never brought to a significant increase in overall survival, it has a positive impact on tumor downstaging, lending to less demolitive CRS. Low peritoneal carcinomatosis diffusion and less aggressive surgery are directly related to lower morbidity rate and seem to be related to better outcome.

Due to the rarity of the disease, the optimal surgical and comprehensive management of this tumor is still a matter of clinical investigations. Furthermore, the cellular and molecular bases of its proliferative potential and resistance to therapy are still poorly understood. Only in the very last years, as treatment options have expanded, there has been a growing interest in this DMPM on part of basic science investigators.¹⁴ On the other hand, this strategy is still weighted by high morbidity and mortality rate, especially if patients present a high tumor burden which requires multiple visceral resections and peritoneectomy procedures.

In the last period we also investigated Ki-67 expression in surgical specimens of the treated patients using Ki-67 labeling index (Ki-67 LI): it was calculated by counting the numbers of positive nuclei per 100 in four different sections. Antigen Ki-67 is a nuclear protein that is associated with and may be necessary for cellular proliferation. MIB-1 is used in clinical applications to determine the Ki-67 labeling index (from 0% to 100%). Some studies on DMPM²², reported a relationship between Ki-67 labeling index and tumor biological features. In fact, low Ki-67 value seems to be related to less aggressive tumor behavior.

In this study, preliminary results of this approach in 42 patients affected by DMPM, treated by cytoreductive surgery and the semi-closed HIPEC technique are reported, with special regard to postoperative complications and survival impact of patients’ selection policy.

Materials and methods

Between June 1996 and November 2011, 308 patients underwent cytoreductive surgery followed by HIPEC for peritoneal carcinomatosis of different origin. DMPM was diagnosed in 42 patients who were included in the present study (24 male and 18 female). The mean age was 52 years (range 19-68 years).

General selection criteria

The preoperative evaluation always included thoracic and abdominal CT scan to stage the peritoneal disease and exclude distant metastases; PET scan is sometimes performed as additional tool in order to detect eventual secondarisms. Upper digestive endoscopy and colonoscopy generally completed the tumor staging. A careful pre operative evaluation of patient’s general condition was always performed and included complete blood tests, electrocardiogram, cardiac ultrasound and spirometry. The presence of not-resectable hepatic metastases or extraabdominal disease, massive ileum involvement and age over 68 years were considered contraindications to the treatment. Informed consent was obtained from all the patients.
Peculiar selection criteria

Diagnostic laparoscopy was performed on 10 patients without a diriment radiologic assessment for possible complete cytoreduction (especially ileum involvement) or to evaluate the response to "neoadjuvant" systemic chemotherapy. Laparoscopy was performed using single-port technique with trocar placement on the midline in order to allow easy removal of the trocar site during subsequent laparotomic access. PCI index was determined according to Sugarbaker's criteria.\textsuperscript{15}

Antigen KI-67 is a nuclear protein associated with cellular proliferation. In literature, low KI-67 labeling index seems to be related to less aggressive tumor behavior. In the last 7 patients affected by DMPM, KI-67 labeling index was performed. We performed directly CRS + HIPEC in patients presenting a MIB-1 lower than 10%, meaning a low cellular proliferation rate and a not massive ileum involvement. On the other hand, we preferred to perform "neoadjuvant" systemic chemotherapy with platinum and pemetrexed in patients presenting a MIB-1 value higher than 10% in order to downstage the tumor burden and subsequently submit them to CRS+HIPEC.

Surgical technique

Just after laparotomy, a complete intraoperative staging of the peritoneal disease was performed using PCI that varies from 0 to 39, where 0 means absence of disease.\textsuperscript{15}

The peritonectomy procedure was performed according to the Sugarbaker criteria:\textsuperscript{16} central peritonectomy; left upper quadrant peritonectomy; right upper quadrant peritonectomy; lesser omentum peritonectomy; pelvic peritonectomy with en bloc removal of pelvic peritoneum, sigmoid colon, rectum, uterus and salpingooophorectomy and peritonectomy of lateral abdominal wall. Implants on the visceral serosa were removed by electrosurgical local dissection.

Peritonectomy procedures were variously combined with resections of the viscera with tumor involvement. A variable number of visceral resections (bowel, greater omentum, hystero-oophorectomy, cholecystectomy, spleen resection) were performed.

The completeness of cytoreduction (CC) was classified according to the Sugarbaker criteria\textsuperscript{17} as: CC-0 (no residual tumor); CC-1 (no residual nodules greater than 2.5 mm in diameter); CC-2 (no residual nodules greater than 25 mm) and CC-3 (residual nodules greater than 25 mm).

HIPEC technique

HIPEC was performed according to the original "semi-closed" abdomen technique\textsuperscript{18} with 5 drain tubes placed in the abdominal cavity, the two y-shaped inflow tubes presenting multiple openings. Backhaus forceps are used to close the cranial and caudal portions of the abdominal wound. The skin is then suspended on a self-retaining retractor, placed at more or less 15 cm from the abdomen by plastic self-blocking strings. This kind of placement creates the virtual cavity needed to perform HIPEC. The central portion of the wound is also suspended by the retractor and covered with a laparoscopic device with a hole in the middle. The drain tubes are connected to a perfusion system formed by two pumps and a heat exchanger to heat the perfusion liquid. The pumps (inflow and outflow) are connected through a reservoir in order to achieve a continuous circulation of the perfusate at a speed of approximately 1 L/min. The pumps are controlled by a computerized system that allows checking of the flow rate and the temperature of the heat exchanger. Three intraperitoneal temperatures, (inflow, outflow, and esophageal temperatures) are checked by probes. The volume of circulating perfusate (solution for peritoneal dialysis) is calculated according to the patient's body surface. During perfusion, the surgeon mixes the perfusate by hand through the hole in the sterilidrape. When the ideal intraperitoneal temperature is reached, the drugs are added to the circuit and HIPEC is
performed for 60 minutes. The drugs used were: cisplatin (CDDP) 100 mg/sm and doxorubicin 16 mg/sm, at a temperature of 41.5 °C. The mean duration of surgery (including HIPEC) was 9 hours (range 5-16). At the end of the operation, the patients were admitted to intensive care unit and then returned to the surgical department when cardiovascular and pulmonary functions became stable.

Follow-up and statistical analysis

After discharge, some patients received systemic chemotherapy. Follow-up was every 3 months for the first year and every 6 for the following 4-5 years. It consisted of abdominal and pelvic exam, abdominal and thoracic CT scan, tumor marker (CA-125) control and additional analysis depending on symptoms presented.

Data of all patients who completed the treatment (CRS and HIPEC) were included in a database. For the analysis of postoperative morbidity rate, all surgical and nonsurgical complications that occurred during the hospitalization period were considered. Postoperative complications were evaluated according to the Dindo-Clavien classification. Overall survival was calculated from the date of surgery to death, regardless of the cause. Kaplan-Meier survival estimates were compared with the log-rank test. All the variables with a P<0.05 were considered statistically significant.

Results

The study included 42 patients (24 male and 18 female). The mean age was 52 years (range 19-68 years). Mean PCI at the time of surgery was 13 (range 4-34). Neoadjuvant treatment by systemic chemotherapy was performed on 16 patients (38.1%); in 6 of them, chemotherapy schedule was based on platinum and pemetrexed. Subocclusive syndrome was diagnosed in 8 patients (19%) during preoperative assessment. Ascites was detected intraoperatively in 28 patients (66.7%). A variable number of visceral resections (bowel, greater omentum, hyster-o-oophorectomy, cholecystectomy, spleen omentectomy) were combined with multiple peritoneotomies: 36 central, 19 right upper quadrant, 11 left upper quadrant, 37 pelvic, 14 left abdominal wall, 12 right abdominal wall peritoneotomies. One bowel anastomosis was performed in 24 patients (57.2%), 2 in 9 patients (21.4%) and in 9 cases no bowel anastomosis was performed (21.4%). In 23 (54.7%) cases the anastomosis was protected with lateral temporary ileostomy, in 5 patients (11.9%) a definitive colostomy was performed. Peritoneotomy involved a mean of 4 sites, a mean of 3 viscera were resected during CRS.

Cytoreduction was complete in 38 patients (90.4%); 22 patients (52.4%) were classified as CC-0, 16 patients (38.1%) as CC-1; incomplete cytoreduction (CC-2) was registered in 4 patients (9.5%). Histologic assessment was indicative of multicystic peritoneal mesothelioma in 7 patients (16.7%) and epithelial mesothelioma in 35 patients (83.3%). Histologic lymph-nodal involvement was detected in 2 patients (4.8%). Mean hospital stay was 23 days (range 9-41 days). Sixteen patients (38.1%) were treated by adjuvant systemic chemotherapy after CRS and HIPEC.

The overall morbidity rate was 35.7% but major complications (grade III-IV according to Dindo-Clavien classification) occurred in only 23.8% (10/42 patients). Surgical reintervention was necessary in 3 patients (7.1%). Overall perioperative mortality rate was 7.1%. If we consider our entire casuistry, we must observe that severe complications are not homogeneously distributed in our experience. In fact, we observed that major morbidity and mortality rates are concentrated in our early experience (the first 25 patients), with severe morbidity rate of 28.0% (7/25) and mortality rate of 12% (3/25). In our later experience (17 patients), severe morbidity rate decreased till 17.0% (3/17) and mortality rate was 0%.

Median overall survival was 65 months, associated to a 1, 3 and 5-year survival rate of 83%, 63% and 44%, respectively.


Discussion

DMPM is a rare and malignant tumor arising from the mesodermal tissue. In recent years the association with asbestos exposure has been consistently observed. Although causal association with asbestos is now accepted, pathogenesis still remains unclear. DMPM represents an aggressive form of disease, leading to a rapid course which is further worsened by an almost persistently late diagnosis. In a review of the literature, no dominant therapeutic guidelines for peritoneal mesothelioma are found. Most articles are clinic-pathological retrospective reviews or case reports compiling disparate therapeutic experiences, including the use of systemic chemotherapy, whole abdominal radiotherapy and intra-abdominal treatments with compounds such as colloidal radioactive 32P and 198Au, thiopeta and bleomycin. Recent reports show a more systematic approach to peritoneal mesothelioma based on debulking surgery and systemic chemotherapy including paclitaxel, cisplatin, or doxorubicin. Any way prognosis seems to be poor if the treatment of DMPM is based on systemic chemotherapy alone, even if associated to palliative surgery. On the contrary, the management of these patients by CRS and HIPEC brought to some good results in terms of prognosis. On the other hand, this strategy is still weighted by high morbidity and mortality rate; for this reason a strict patients' selection policy is mandatory.

The median survival reported in literature ranges from 7 to 13.5 months and only a few long-term survivors are reported. The median overall survival reported in our study is 65 months, with a 3-year survival rate of 63%. These results need to be interpreted with caution due to a high selected treated population. In fact, in our institution, in order to reach better results in terms of prognosis and to minimize morbidity and mortality rates, the evolution of CRS and HIPEC as treatment of DMPM was based on a severe patients' selection policy.

The preoperative workup evaluation of ileum involvement and carcinomatosis diffusion often included an explorative laparoscopy. This procedure allowed to discriminate patients suitable to immediate complete CRS and HIPEC from those who could benefit from a neoadjuvant systemic chemotherapy with platinum and pemetrexed in order to downstage burden disease. Patients not eligible at first step to CRS and HIPEC who had undergone neoadjuvant systemic chemotherapy were often submitted to a second explorative laparoscopy, in order to confirm the downstaging of peritoneal carcinomatosis and the feasibility of a complete cytoreduction.

Some studies on DMPM reported a relationship between Ki-67 labeling index and tumor biological features. In fact, low Ki-67 value seems to be related to less aggressive tumor behavior. In the last 7 patients affected by DMPM, the Ki-67 labeling index was determined.

This evaluation was useful, in our late experience, to improve our patients' selection policy. In fact we observed that if MIB-1 value was lower than 10%, meaning a low cellular proliferation rate and the ileum was not massively involved at preoperative laparoscopy, the probability to obtain an optimal cytoreduction was high. In those cases we performed directly CRS and HIPEC. On the other hand, if MIB-1 index was higher than 10% and/or a massive ileum involvement was present with a widespread disease diffusion (high PCI), we preferred to perform "neoadjuvant" systemic chemotherapy; these patients were then submitted to CRS and HIPEC, often performing a second explorative laparoscopy before the procedure.

In our institution, the evolution of DMPM treatment was based on a severe patients' selection policy. In fact, MIB-1 determination, preoperative determination of ileum involvement by laparoscopy and evaluation of the response to neoadjuvant systemic chemotherapy allowed to perform CRS and HIPEC in highly selected patients, obtaining encouraging results in terms of overall survival and postoperative morbidity.
authors of nearly 100 cases. We must underline that strict selection criteria applied during our late experience, associated to an improved experience in the intraoperative and postoperative patients' management brought to lower incidence of severe postoperative morbidity (from 28% to 17%) and allowed to reduced mortality rate (from 12% to 0%).

**Conclusions**

Complete surgical cytoreduction associated with HIPEC shows encouraging results in terms of overall survival and acceptable complication and mortality rates in DMPM treatment. The best results are achieved in patients presenting low peritoneal disease diffusion in which a complete cytoreduction was obtained before HIPEC. Good results are achieved too in patients presenting a massive peritoneal involvement submitted to neoadjuvant systemic chemotherapy based on platinum and pemetrexed, in order to downstage the peritoneal carcinomatosis diffusion.

In order to improve selection criteria of patients who may benefit from CRS and HIPEC as “frontline treatment” instead of a neoadjuvant systemic chemotherapy, promising results may come from preoperative Ki-67 labeling index evaluation. Moreover these results should be confirmed by randomized trials in order to evaluate the impact both of complete cytoreductive surgery and HIPEC.

**Riassunto**

Trattamento del mesotelioma peritoneale maligno mediante citodissezione chirurgica e HIPEC

Obiettivo. Il mesotelioma peritoneale maligno diffuso (DMPM) è un tumore raro e localmente aggressivo con prognosi infastidita, legato, nella maggior parte dei casi di esposizione all’amianto. La frequenza è in aumento, ma, al momento, nessuna terapia standard è ancora disponibile. La biologia di questa malattia è ancora poco conosciuta. Diversi centri altamente specializzati hanno recentemente riportato un miglioramento della sopravvivenza mediante un innovativo approccio loco-regionale.

Lo scopo di questo articolo è quello di valutare il beneficio in termini di sopravvivenza e la morbilità dei pazienti affetti da DMPM trattati presso il nostro Istituto mediante chirurgia citodissezitiva (CRS) associata a chemioterapia intraperitoneale e HIPEC.

**Metodi.** Lo studio comprende 42 pazienti affetti da DMPM trattati mediante approccio uniforme costituito da chirurgia citodissezitiva associata ad HIPEC a base di cisplatino e doxorubicina. L'end point primario è stato la sopravvivenza globale ed il tasso di morbidità. L'end point secondario è stato, invece, la valutazione dei fattori prognostici per la sopravvivenza globale.

**Risultati.** Il follow-up medio è stato di 72 mesi (range 1-235 mesi). Trentacinque pazienti (83,3%) sono risultati affetti da mesotelioma di tipo epiteliale e 7 pazienti dall'istotipo multicistico. L'indice medio di cancro peritoneale (PCI) è stato 13. Trentotto pazienti (90,4%) hanno ottenuto una citodissezione completa (CC-0/1). Il tasso di morbidità complessiva è stato del 35,7% associato ad una mortalità perioperatoria del 7,1%. La sopravvivenza globale mediana è stata di 65 mesi con un tasso di sopravvivenza a 3 e 5 anni del 63% e 44%, rispettivamente.

**Conclusioni.** Il trattamento di DMPM mediante CRS + HIPEC in pazienti selezionati è una tecnica realizzabile che permette di ottenere risultati incoercibili in termini di tasso di sopravvivenza globale, con una percentuale di morbidità accettabile. Ulteriori indagini sono necessarie per chiarire quale sia il ruolo e la tempestiva migliore per realizzare questa tecnica promettente.

Parole chiave: Mesotelioma - Amianto - Carcinoma - Febbre.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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