

An Italian Multicentric Phase II Study on Peritonectomy and Intra Peritoneal Hyperthermic Perfusion (IPHP) to Treat Patients with Peritoneal Mesothelioma

Deraco M¹, De Simone M.², Rossi C.R.³, Cavaliere F.⁴, Difilippo F.⁴, Scuderi S.⁵, Pilatti P.³ and Kusamura S.⁶

Dept. of Surgery¹, Melanoma Sarcoma Unit, Istituto Nazionale per lo studio e la cura dei tumori, Milan, Italy, Dept. of Surgery², Surgical Oncology Unit, Ospedale San Giuseppe, Empoli, Italy, Clinica Chirurgica II³, Ospedale dell'Università di Padova, Dept. of Surgery⁴, Polo Oncologico Istituto Regina Elena, Rome, Italy, Advanced Surgical Oncology Center⁵, Ospedale S. Giovanni Battista, University of Turin, Turin, Italy, Dept. of Surgery⁶, Gynecologic Oncology Unit, Istituto Nazionale per lo studio e la cura dei tumori, Milan, Italy

Peritoneal mesothelioma (PM) is a rare disease, with a poor prognosis. We decided to prospectively evaluate the prognostic impact and the morbimortality of cytoreductive surgery combined with intraperitoneal hyperthermic perfusion in the treatment of this clinical entity.

Sixty one patients with PM (31 males and 30 females) were enrolled onto a Phase II multicentric clinical trial. The mean age was 51 years (range: 24-72). CRS was performed with peritonectomy procedures. The closed, opened and semi-closed abdomen techniques were employed for IPHP using cisplatin plus mitomycin-C or cisplatin and doxorubicin for 60/90 minutes under hyperthermic conditions (42.5°C). One patient was operated on twice because of disease recurrence. Mean follow-up was 20 months (range: 0.1-76).

Forty six (74%) patients were optimally cytoreduced. Five-year overall and 5 yr progression-free survivals were 54% and 37%, respectively. Completeness of cytoreduction was significantly associated with outcome. Twenty Grade III complications occurred in 14 (23%) patients and the most frequent one was digestive fistula/perforation (11%). No treatment-related mortality was recorded.

CRS + IPHP was proven to be acceptable in terms of morbidity and mortality in patients with PM and suggest a positive impact on outcome. Further prospective controlled studies are warranted to confirm these results.

Key Words: Peritoneal mesothelioma, Peritonectomy, Intraperitoneal hyperthermic perfusion

Peritoneal mesothelioma (PM) is a rare tumour, accounting for 10% to 20% of the 2200 cases of malignant mesothelioma registered each year in the United States (1,2).

The prognosis for patients with PM is poor, with a median overall survival of 12.5 months in the best series (3). A variety of treatment options have been proposed, alone or in combination, but most have failed to palliate or to change the final outcome. The mechanism of death is related to intraperitoneal progression and the disease remains in the abdominal cav-

ity for most of its natural history (4). This pattern of spread would seem to indicate the potential usefulness of selectively increasing drug concentration in the tumour-bearing area by direct intraperitoneal chemotherapy instillation (5). The advent of locoregional therapy resulting from the combination cytoreductive surgery and intraperitoneal hyperthermic perfusion has changed dramatically the approach to this clinical entity. Phase I/II investigations on CRS+IPHP provided promising results when it was employed in a salvage setting for patients with PM (6-8), as long-

term survivors have been reported.

The aim of this multicentric Phase II clinical study was to evaluate this therapeutic approach in patients with malignant PM in terms of toxicity, morbidity and survival.

Patients and Methods

In accordance with study design, patients were considered suitable for recruitment after a complete evaluation including clinical examination, chest-abdominal-pelvic CT scan, ultrasonography and tumour markers (CEA, Ca125, CA19.9).

Eligibility criteria included: confirmed histological diagnosis of peritoneal mesothelioma; age < 75 years; PS (WHO) ≤ 2 ; good cardiac, renal, hepatic and bone marrow functions; no concomitant evidence of pleural extension; no other concomitant neoplasms and informed written consent to participate in the study.

The studied group included patients with PM referred to 4 Italian Oncological centres: Istituto Nazionale per lo studio e la cura dei tumori (Milan), Polo Oncologico Istituto Regina Elena (Rome), Clinica Chirurgica Università di Padova (Padua), Ospedale S. Giovanni Battista, University of Turin, from August 1995 to September 2003. Sixty one (31 males and 30 females) patients were enrolled onto the study. The mean age was 51 years (range 24-72). One patient was operated on twice because of disease recurrence. Twenty one (34%) patients had received systemic chemotherapy before the procedure.

Cytoreductive surgery. The techniques of cytoreductive surgery have been described previously (7). Briefly, the surgical procedure was carried out with one or more of the following steps, depending on disease extension: 1) greater omentectomy, right parietal peritonectomy \pm right colon resection; 2) pelvic peritonectomy \pm sigmoid colon resection \pm hysterectomy; 3) lesser omentectomy and dissection of the duodenal-hepatic ligament \pm antrectomy \pm colecystectomy; 4) right upper quadrant peritonectomy with Glissonian's capsule; 5) left upper quadrant peritonectomy \pm splenectomy; 6) other intestinal resection and/or abdominal mass resection. A ball-tip electro-surgical handpiece was used to dissect the tumour on peritoneal surfaces from normal tissue. The electro-surgery was used on pure cut at high voltage. The 2 mm ball-tip electrode was used for dissecting on visceral surfaces, including stomach, small bowel, and colon. The timing of intestinal anastomoses (after or before the cytoreduction) for patients who underwent bowel

resections as well as the performance of diverting ostomies were decided at the each surgical staff discretion. Cytoreduction was classified into 3 levels according to the number of procedures performed: level I - 1- 2 procedures; level II - 3 or 4 procedures; level III – more than 5 procedures.

Peritoneal carcinomatosis was quantified according to Peritoneal Cancer Index (PCI) (8). Accordingly, the mean PCI was 24 (range: 2 to 36). Residual disease after surgery was classified according to Sugarbaker criteria (8): optimal cytoreduction=residual disease <2.5 mm; suboptimal cytoreduction=residual disease >2.5mm.

Intraperitoneal hyperthermic perfusion. After CRS, the IPHP was performed according to the opened (18), semi-closed (9) and closed abdominal techniques (10). In order to perform continuous peritoneal temperature monitoring during IPHP, thermocouples were placed in the abdominal cavity. The pre-heated polysaline perfusate containing cisplatin (CDDP: 25 mg/ m²/l) plus mitomycin-C (MMC: 3.3 mg/m²/l) or cisplatin (CDDP: 43 mg/l) plus doxorubicin (Dx: 15.25 mg/l) (11) was instilled into the peritoneal cavity using a heart-lung pump at a mean flow of 600 ml/min for 60 minutes starting from the true hyperthermic phase (42.5°C). At the end of perfusion, the perfusate was rapidly drained and the abdomen closed after careful intra-cavitary inspection.

Follow-up and statistical analysis

In the postoperative period, patients were assisted in an Intensive Care Unit (ICU) for at least 5 days and assessed daily with laboratory and imaging exams. Long-term follow-up was carried out by physical examination, tumour marker monitoring, thoracic and abdominal CT scan every 6 months in the first 2 years and every 12 months, thereafter. Overall survival was calculated from the date of surgery to date of death or time of last follow-up; progression free survival was calculated from the date of surgery to date of disease progression, or date of death whichever occurred first. A Kaplan-Meier survival curve was fitted to the data and tested using a log-rank test for differences between curves.

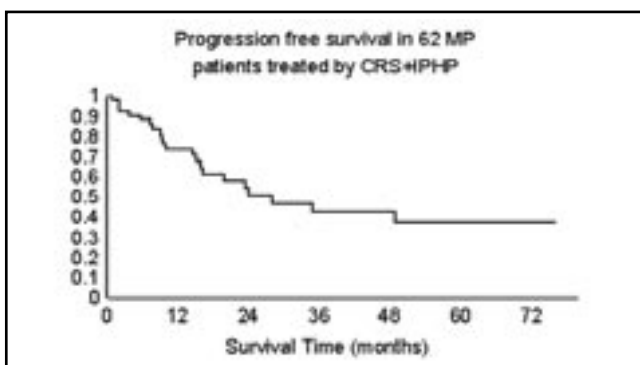
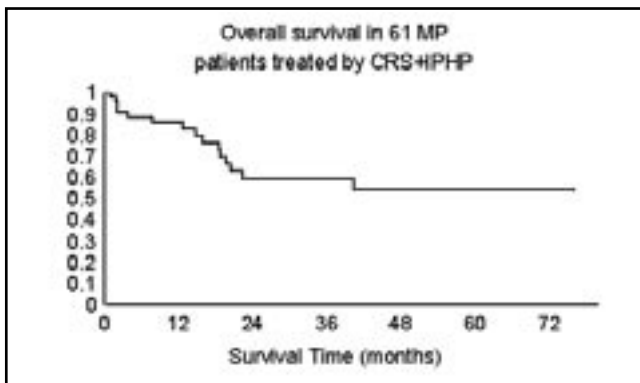
Evaluation of morbidity, toxicity and mortality. Grading of complications was performed according to the following criteria: GI: no complications, GII: minor complications, GIII: major complications (requiring reoperation or Intensive care unit admission or interventional radiology and GIV: in hospital mortality. Grading of toxicity was performed according to the WHO criteria. We considered only those unfavourable events occurring within the 28th day after the procedure.

Results

Twenty nine (47%), 19 (31%) and 8 (8%) cases were submitted to level III, II and I procedures respectively. Forty six (74%) patients were optimally cytoreduced. Nineteen cases were submitted to bowel anastomoses.

Twenty grade III complications were observed in 14 (23%) cases. They were as follow: 8 digestive fistula, 2 grade IV renal failure, 2 pulmonary embolism, 2 severe infection sepsis, 1 disseminated intravascular coagulation, 1 grade III leucopenia, and 4 other types. No treatment related death was observed. IPHP-related grade III/IV toxicity occurred in 5 (8%) of the cases. They were as follow: 1 haematological grade III, 2 renal grade IV, 1 renal grade III and 1 alopecia grade III.

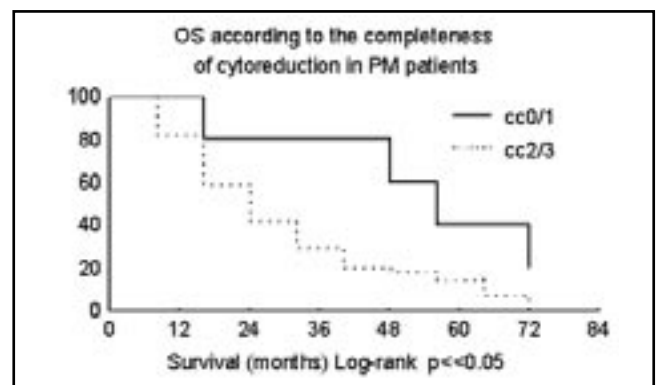
Five-year overall survival (OS) was 54%. Five-year progression-free survival (PFS) was 37%. The median PFS was 28 months (Figures 1 and 2). At the end of study period the final disease status was as follow: 30 patients with no evidence of disease (NED), 16 patients were alive with disease (AWD) and 15 had died of disease. Only the completeness of cytoreduction presented a statistically significant link with the survival ($p < .05$) (figure 3).



Discussion

Although the median survival of patients with PM reported in most series is short, long-term survival has been described following intraperitoneal 32P combined with whole abdominal radiation (12). Lederman et al (13) reported the results on 10 patients treated with sequential debulking, chemotherapy (5 intraperitoneal and 1 intravenous) and whole abdominal irradiation and obtained a complete remission at 19+ to 78+ months of follow-up. Conversely, those who did not receive this combined approach were dead at 2 to 15. Similar results were obtained by Langer et al.(14), suggesting the relative role of surgical debulking on outcome. However, it is impossible to conclude that any treatment improves outcome over surgical cytoreduction alone as these studies were conducted on small series of patients, with a short follow-up, ill-defined eligibility criteria with the inclusion of patients with pleural disease, and absence of control groups. The combination of CRS and IPHP is an innovative treatment strategy that has evolved over the last 2 decades in the treatment of peritoneal surface malignancies with good results according to phase II (15) and III (16) clinical trials. The rationale concerning the attainment of a synergistic effect between chemotherapies and heat as well as the pharmacokinetics advantage of locoregional instillation of antitublastic drugs was outlined elsewhere (17).

We observed in our study that the completeness of cytoreduction presented a significant impact on survival. Patients with optimal cytoreduction (residual disease <2.5mm) presented a median OS of 56 months while those sub optimally cytoreduced presented a median OS of 24 months ($p < .05$). Whether this apparent survival benefit resulted from lower tumour aggressivity or from the surgical effort is difficult to ascertain. An answer to such a question should be provided by another study with a different well formulated design. Nevertheless this finding is alignment with



experimental evidence that support one of eligibility criteria for IPHP. Usually the drugs, even when instilled intrabdominally, are not able to penetrate tumour tissue deeper than a few cellular layers, so that the volume of residual disease remains one the major factor influencing the efficacy of locoregional therapy. Moreover, residual disease was proven to be a prognostic factor in PM, treated by CRS+IPHP (**Errore. Il segnalibro non è definito.**,18). On the hand, in contrast with the findings of other authors (**Errore. Il segnalibro non è definito.**,18), univariate analysis of prognostic factors showed that sex and extension of carcinomatosis, quantified by PCI criteria, were not predictive of survival. This finding is not surprising and could be attributed to the small sample size of our casuistic and different distribution other prognostic factors between the study groups.

A number of reports in the literature on the treatment of PM with CRS and IPHP have demonstrated encouraging results. Park et al.(6) treated 18 patients with primary PM with surgical debulking and IPHP. The primary endpoints were the definition of dose-limiting toxicity and maximum tolerated dose (MTD) of CDDP administered via a 90-minute continuous hyperthermic peritoneal perfusion (CHPP), initially alone and then with escalating doses of TNF. Two-year OS was 80% and a median PFS of 26 months. There was no treatment-related mortality and overall operative morbidity was 24%.

Sebbag et al. treated 33 PM patients with CRS and perioperative intraperitoneal chemotherapy (cisplatin+doxorubicin) (**Errore. Il segnalibro non è definito.**). Median survival was 31 months and overall survival at 3 years was 56%. The morbidity rate was 33% and perioperative mortality was 3%.

Loggie et al. conducted a prospective clinical trial in which 12 patients with PM underwent CRS followed by a 2-hour closed low-volume intraoperative intraperitoneal heated chemotherapy (IPHC) using mitomycin C (**Errore. Il segnalibro non è definito.**). One patient died due to small bowel perforation 50 days after the procedure. Haematological toxicity of the procedure was minimal. Ascites was controlled in all patients and permanently resolved in 86% of patients presenting with this sign. Median survival was 34.2 months.

In our previous experience we reported on 19 PM patients submitted to 20 consecutive procedures of CRS+IPHP. We observed a 3-year overall and progression-free survivals of 69% and 66%, respectively. The operative morbidity (grade II/III), mortality and overall toxicity (grade I-IV) rates were 25%, 0% and 30%,

respectively. Seventeen (94%) out of 18 patients had resolution of ascites (17).

The results of the present study do not differ from these literature data. The low treatment-related mortality/morbidity indicates that CRS + IPHP is a feasible and safe option for patients with PM. Furthermore, in comparison with historical controls (2,3,19), the achievement of a 54% 5-year overall survival suggests that this new approach is a potentially effective treatment for selected patients with PM. Although the low incidence of PM constitutes the major drawback for the completion of a randomized Phase III clinical trial in a timely fashion, it is imperative to confirm our findings through further prospective controlled studies.

References

1. Connelly R.R., Spistas R., Myers M.H., et al.: Demographic patterns for mesothelioma in the United States. *J. Natl. Cancer Inst.* 78:1053, 1987.
2. Antman K., Osteen R., Klegar K., et al.: Early peritoneal mesothelioma: a treatable malignancy. *Lancet* 11:977-981, 1985.
3. Weissmann L., Osteen R., Corson J., Herman T., Antman K.: Combined modality therapy for intraperitoneal mesothelioma. *Proc. Am. Soc. Clin. Oncol.* 7:274, 1988.
4. Deraco M., Santoro N., Carraro O., Inglese M.G., Rebuffoni G., Guadagni S., Somers D.C. and Vaglini M.: Peritoneal carcinomatosis: Feature of dissemination. A review. *Tumori* 85:1-5, 1999.
5. Markman M., Kelsen D.: Efficacy of cisplatin-based intraperitoneal chemotherapy as treatment of malignant peritoneal mesothelioma. *J. Cancer. Res. Clin. Oncol.* 118:547-550, 1992.
6. Park B.J., Alexancer H.R., Libutti S.K., Wu P., Rolyalty D., Kranda K.C., and Bartlett D.L.: Treatment of Primary Peritoneal Mesothelioma by Continuous Hyperthermic Peritoneal Perfusion (CHPP). *Ann. Surg. Oncol.* 6:582-590,1999.
7. Sugarbaker P.H.: Peritonectomy Procedures. *Ann. Surg.* 1995;221:29-42.
8. Jacquet P., and Sugarbaker P.H.: Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. *J. Exp. Clin. Cancer Res.* 15:49-58, 1996.
9. De Simone M., Barone R., Vaira M., Aghemo B., Mioli P., Franco C., Scuderi S., Costamagna D., Dei Poli M.: Semi-closed hyperthermic-antiblastic peritoneal perfusion (HAPP) in the treatment of peritoneal carcinosis. *J. Surg. Oncol.* Feb;82(2):138-40, 2003.
10. Glehen O., Osinsky D., Cotte E., Kwiatkowski F., Freyer G., Isaac S.,Trillet-Lenoir V., Sayag-Beaujard A.C., Francois Y., Vignal J., Gilly F.N.: Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery

- for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. *Ann. Surg. Oncol.* Oct;10(8):863-9, 2003.
11. Rossi C.R., Foletto M., Mocellin S., Pilati P., De S.M., Deraco M., Cavaliere F., Palatini P., Guasti F., Scalerta R., Lise M.: Hyperthermic intraoperative intraperitoneal chemotherapy with cisplatin and doxorubicin in patients who undergo cytoreductive surgery for peritoneal carcinomatosis and sarcomatosis: phase I study. *Cancer.* Jan 15;94(2):492-9, 2002.
 12. Cain J., Nori D., Huvos A., Erlandson R.A., Hilaris B., Lewis J.L. Jr.: The role of radioactive colloids in malignant peritoneal mesotheliomas. *Gynecol. Oncol.* Oct;16(2):263-74, 1983.
 13. Lederman G.S., Recht A., Herman T., and et al.: Long-term survival in peritoneal mesothelioma: the role of radiotherapy and combined modality treatment. *Cancer* 59:1882-1886, 1987.
 14. Langer J.C., Roseblum N., Hogan M., Nash S., Bagchi P., LaCreta F.P., Catalano R., Comis R.L., O'Dwyer P.J.: Intraperitoneal cisplatin and etoposide in peritoneal mesothelioma: favorable outcome with multimodality approach. *Cancer Chemother. Pharmacol.* 32:204-208, 1993.
 15. Cavaliere F., Di Filippo F., Cosimelli M., Aloe L., Arcuri E., Anza M., Callopoli A., Di Lauro L., Morace E., Botti C., Natoli S., Tedesco M., Giunta S., Cavaliere R.: The integrated treatment of peritoneal carcinomatosis. A preliminary experience. *J. Exp. Clin. Cancer Res.* 18:151-8, 1999.
 16. Verwaal V.J., van Ruth S., de Bree E., van Sloothen G.W., van Tinteren H., Boot H.: Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J. Clin. Oncol.* 21:3737-43, 2003.
 17. Deraco M., Casali P., Inglese M.G., Baratti D., Pennacchioli E., Bertulli R., Kusamura S.: Peritoneal mesothelioma treated by induction chemotherapy, cytoreductive surgery, and intraperitoneal hyperthermic perfusion. *J. Surg. Oncol.* Jul;83(3):147-53, 2003.
 18. Sugarbaker P.H., Welch L.S., Mohamed F., Glehen O.: A review of peritoneal mesothelioma at the Washington Cancer Institute. *Surg. Oncol. Clin. N. Am.* Jul;12(3):605-21, xi, 2003.
 19. Antman K., Pomfret E., Aisner J., McIntyre J., Osteen R.T., Greenberger J.S.: Peritoneal mesothelioma: natural history and response to chemotherapy. *J. Clin. Oncol.* 1:386-391, 1983.

Marcello Deraco, M.D.

Unità Operativa Melanoma e Sarcoma

Istituto Nazionale per lo Studio e la Cura dei Tumori

Via Venezian, 1 - 20133 Milan, Italy

Tel +39 02 23902362; Fax +39 02 23902404

E-mail: marcello.deraco@istitutotumori.mi.it