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120 Peritoneal Carcinomatoses from Colorectal Cancer Treated with Peritonectomy and Intra-abdominal Chemohyperthermia: A S.I.T.I.L.O. Multicentric Study

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Abstract. *A multicentric study has been carried out on 120 patients affected by peritoneal carcinomatosis from colorectal cancer. Patients have been treated by cytoreductive surgery and intra-operative hyperthermic chemoperfusion (HIPEC) with cisplatin (CDDP) and mitomycin-C (MMC). A small group of patients were treated with oxaliplatin (LOHP) following the Elias et al. scheme [intravenous 5-fluorouracil (400 mg/m^2) and leucovorin (20 mg/m^2) followed by intraperitoneal perfusion with LOHP (460 mg/m^2) in 2 l/m^2, during 30 min at 43˚C]. CC-0 cytoreduction was achieved in 85.2% of the patients. Major morbidity and mortality was 22.5% and 3.3%, respectively. No G4 toxicity was registered. The three-year survival was 25.8%. The difference in survival evaluating complete cytoreduction (CC-0) vs. incomplete (CC1-2; residual tumor nodules greater than 2.5 mm) was statistically significant ($p<0.0001$). Evaluating only the patients that could be cytoreduced to CC-0, the 3-year survival was raised to 33.5%. In our experience the peritoneal cancer index (PCI) has been demonstrated to be a weak prognostic factor reaching a statistical significance only after the exclusion of patients with resected hepatic metastases. The patients treated with oxaliplatin were alive and free-of-disease after a 16-month median follow-up.*

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The peritoneum, together with the liver, are the most likely sites of recurrence after colon carcinoma resection with curative intent, with a frequency rate of 25-35% (1). In 25% of the patients the relapses are sited on the peritoneum (2) allowing 7 months of median survival time (3). The combination of fluorouracil and leucovorin has been widely used to treat metastatic colorectal cancer with disappointing results. In the last few years new agents have been utilized to treat advanced colorectal carcinoma, achieving an objective response rate of over 50% with an overall survival rate of 15-18 months (4, 5) with up to 50% grade 3-4 toxicity.

The natural history of the patients with peritoneal recurrences have prompted new locoregional aggressive approaches, combining peritonectomy procedures and intraperitoneal chemotherapy. Exciting results have emerged from a series of phase II studies, in which the 3-year survival ranged from 22% to 65% (6-8), and a recent phase III study comparing cytoreduction associated with intra-operative hyperthermic chemoperfusion (HIPEC) *vs.* debulking surgery followed by systemic chemotherapy, which demonstrated a significantly better survival for the HIPEC group (9).

However, in spite of the advantage of the survival rate obtained with the integrated treatment, many questions remained unanswered regarding the selection of patients and the identification of the predictive prognostic factors. The Italian Society of Locoregional Treatment in Oncology (SITILO) decided in 1996 to study a protocol for the treatment of peritoneal carcinomatosis by means of peritonectomy and HIPEC. The group of patients with peritoneal carcinomatosis of colorectal origin have been the object of the present report.

Patients and Methods

One hundred and twenty patients with peritoneal carcinomatosis of colorectal origin, synchronous (23%) or recurrent after resection of the primary disease with curative intent (73%), who underwent peritonectomy and HIPEC in 6 Italian Institutions between January 1996 and June 2005, represent the study population. The median age was 53 years (range 19-76). Many patients (72%) had been previously treated with adjuvant or palliative systemic chemotherapy, most of them with 5-fluorouracil and leucovorin and then cisplatin, leucovorin, mitomycin-C, oxaliplatin and irinotecan, alone or in various combinations. The surgical technique has been described in detail previously (10). HIPEC was carried out with the "open" or "closed" technique for 60-90 minutes at a temperature of 41.5˚C - 43˚C throughout the abdominopelvic cavity, introducing into the perfusion circuit mitomycin-C (3.3 mg/m^2/L) and cisplatin (25 mg/m^2/L). In the last 18 months, 11 patients in a single center were treated according to the method of Elias *et al.* (11), perfusing oxaliplatin (460 mg/m^2) for 30 minutes at 43˚C, just after intravenous administration of 5-FU (400 mg/m^2) and leucovorin (20 mg/m^2).

Clinical data were recorded onto a standard database form and evaluated by the same author. To study relationships between variables the Chi-square test has been used. Survival analysis was performed with the Kaplan-Meier method, and comparison of curves with the Log-rank test. Standard probability cut-off, $p \leq 0.05$, was chosen as the significance level.

Results

Thirteen percent of the patients showed occlusive symptoms at the time of hospitalization. Two patients developed peritoneal carcinomatosis, 16 and 20 months after resection of liver metastasis, respectively. The peritoneal cancer index (PCI), as described by Sugarbaker *et al.* (13), ranged between 11 and 20 in 54% of the patients and more than 20 in 12%.

The cytoreductive surgery was synchronous with the resection of the primary tumor in 28 patients (23%) or of liver metastasis in 6 (5%). A total peritonectomy was performed in 36 cases (30%) due to the extent of the disease. Complete cytoreduction (CC-0) was achieved in 85.2%, optimal (CC-1) in 7.4%, while in 7.4% of the patients peritonectomy resulted in macroscopic residual tumor with nodules larger then 0.5 cm (CC2-3).

The HIPEC was routinely carried out, except for a few cases because of intra-operative complications. The technique was "open" in 56.7% of the procedures and "closed" in 43.3%, and lasted 90 minutes in 76% and 60 minutes in the remaining 24%.

Major morbidity was 22.5% and was directly correlated with surgical time ($p \leq 0.004$), extension of cytoreduction ($p \leq 0.007$) and PCI ($p \leq 0.02$). The most important adverse events were represented by perforation (5%), anastomotic leakage (3.3%) and infection (3.3%). Locoregional toxicity (Table I), evaluated according to the modified Ozols *et al.* classification (12), was G1 in 21.7% of the patients, G2 in 1.4%, G3 in 1.4% and G4 in 8.3%. The observed systemic toxicity (WHO) was mainly hematologic (G1 in 9.1%, G2 in 8.3% and G3 in 2.5%) and gastrointestinal (G1 in 8% and G2 in 2%). G4 toxicity was not observed. Post-operative mortality was 3.3%.

Table I. *Modified Ozols classification of locoregional toxicity after intraperitoneal chemotherapy.*

Grade	Description
1	Abdominal pain after third post-operative day that requires analgesic drug administration (non-steroidal anti-inflammatory drugs).
2	Abdominal pain after third post-operative day that requires major analgesic drug administration (morphine).
3	Abdominal pain resistant to all analgesic drugs.
4	Leak or perforation.

The 3-year overall survival for the entire series was 25.8% and the median survival was 19 months. No statistically significant survival differences emerged between the patients with synchronous or metachronous peritoneal carcinomatosis ($p \leq 0.07$), while previous resection of hepatic metastases, even before the onset of carcinomatosis, was showed to be a strongly unfavorable prognostic factor associated with 0% 3-year survival ($p \leq 0.01$). At a first analysis no meaningful correlations were evident between PCI and survival; but when only the patients without a history of hepatic metastases were considered, the PCI reached a significant prognostic value ($p \leq 0.02$). Evaluating only the subgroup of patients cytoreduced to CC-0, the 3-year survival raised to 33.5%, and the difference in survival between CC-0 and CC1-2 was highly significant ($p < 0.0001$). Statistically meaningful differences of survival between patients CC-1 and CC-2 did not emerge. No significant differences, either in survival or in recurrence rate, were observed between performing the HIPEC with the "open" *vs.* "closed" technique ($p \leq 0.08$) or modifying the duration of chemoperfusion from 60 to 90 minutes ($p \leq 0.07$). All the patients treated with oxaliplatin according to the Elias *et al.* study protocol were alive and free-of-disease at 16-month median follow-up.

Discussion

The first literature report concerning several patients with colorectal peritoneal carcinomatosis treated by peritonectomy and intraperitoneal chemotherapy, was in 1996: complete cytoreduction and disease limitation to 2 abdominal

quadrants (the abdomen was divided into 4 quadrants above the pelvis) and limited tumor seedings (less than 5 mm of tumor nodules) (13) were considered favourable prognostic factors for the integrated treatment to be administered. The presence of resectable hepatic or lymphnodal metastases had no noticeable impact on survival.

One year later, Portilla *et al.* published the preliminary guidelines for the treatment of colorectal carcinomatosis (14) and defined the following quantitative aspects for the selection of patients to be addressed to the integrated treatment: disease limited to the abdominal and pelvic cavities; resectable disease; small, not confluent implants; involvement of a limited number of abdominal regions and feasibility of a macroscopically complete cytoreduction.

Further phase II studies have not modified such selection approach to peritonectomy which remained dependent on the PCI characteristics. The results of the first phase III trial comparing the integrated treatment *vs.* systemic chemotherapy for colorectal peritoneal carcinomatosis were pubblished in 2003 (9). One hundred and five patients, 87 with colorectal and 18 with appendicular carcinomatosis were enrolled for the 3-year study and randomized to an experimental group (54 patients were treated with peritonectomy and HIPEC for 90 minutes with MMC in fractionated doses of 17.5 - 8.8 - 8.8 mg/m^2, followed by 6 weeks of adjuvant chemotherapy) and a control group (51 patients treated with 5-FU 400 mg/m^2 *i.v.* and leucovorin 80 mg/m^2 *i.v.* weekly for 26 weeks or until progression or unacceptable toxicity). Significantly better survival was reported for the integrated treatment than the systemic chemotherapy and once again the survival correlated with the number of regions involved and the completeness of cytoreduction.

The results of the present study have not differed substantially from the results in the literature, but PCI has acquired prognostic significance only when the patients with resected hepatic metastases, even if previously removed, were excluded from the analysis. However, experimental studies have clearly demonstrated that biomolecular characteristics of the neoplastic cells play the most important role in determining whether haematogenous metastatization rather than peritoneal spreeding occurs (15). Correct evaluation of these biomolecular aspects, as soon as this becomes possible, should be conducted before directing patients to loco-regional integrated treatment. Even if the PCI represents today the most diffuse and reliable classification system, it still does not take account of the specific weight of the hepatic and nodal metastases, and other emerging factors. PCI remains a pre-operative evaluation parameter, that should be potentially modifiable even during the course of the treatment by factors other than simple quantitative analysis, such as a greater or lesser sensibility to chemotherapy.

The use of new drugs in the perfusional regimen should be examined. In particular oxaliplatin, is the most active drug, as a single agent, in the second-line treatment of metastatic colorectal carcinoma and its effect does not depend upon the cellular cycle; moreover, it is synergistic with hyperthermia (16). Recently oxaliplatin has been combined in HIPEC with peritonectomy in a preliminary study on 24 patients with colorectal carcinomatosis (mean PCI 16.9±9.5). The results have shown a satisfactory 3-year survival of 65% (11). As far as our personal experience is concerned, preliminary results appear really encouraging, because of the 100% 2-year survival.

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