Editorial

Splenectomy revisited in 2011: Impact on hematologic toxicities while performing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Peritoneal carcinomatosis of colorectal origin is considered stage IV metastatic disease and is sometimes the only site of distant spread (1). It was once considered a terminal condition with a six-month median survival (2). Since 1980, the concept of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has evolved into at least a reasonable if not a standard treatment for such aggressive disease (3,4). Peritonectomy associated with organ resections was thoroughly described by Sugarbaker to achieve complete macroscopic cytoreduction (5). The addition of HIPEC helps treat residual microscopic disease by providing a high concentration of cytotoxic agents with minimal systemic absorption (6). Hyperthermia potentiates the cytotoxic effects of chemotherapy (7). Mitomycin C (MMC) and oxaliplatin are the most commonly used drugs for non-ovarian malignant peritoneal carcinomatosis (8). The last consensus meeting in Milan addressed adverse effects in CRS + HIPEC agreeing to use National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE V3) standard criteria to grade the complications (9). This extensive procedure comes at a high price of grade III/IV (10) morbidity (12-52%) and early mortality (0.9-5.8%) (11). The main complications with these approaches are infectious, renal, thrombotic and hematologic (12). They are related to the extent of the cytoreduction but also to the local and systemic toxicity of the intra peritoneal chemotherapy.

In this issue, Becher and al. analyzed 195 patients undergoing CRS and HIPEC for carcinomatosis, mainly of appendiceal and colon origin. They compared patients requiring splenectomy to those who did not with the focus of this report on hematotoxicity. The authors are to be congratulated for the complete laboratory and toxicity data, which are often missing or incomplete in the literature. The number of patients studied is significant, highlighting the familiarity and experience with the procedure at the Wake Forest University School of Medicine, Winston-Salem. Three important points can be gleamed from this study. The splenectomy group required more red blood cells transfusions, had a longer hospital stay and they also had a lower incidence of white blood cell toxicity. There was no significant difference in platelet or plasma requirements. These findings can be explained by the fact that patients requiring splenectomy had a more important tumor burden and thus required a more extensive surgery. The white blood cell nadir post HIPEC was statistically higher in the splenectomy group. Hence, granulocyte colony stimulating factor (G-CSF; filigrastim) was needed in only 29% of the splenectomy group compared to 43% of non-splenectomy patients (P=0.043) following their protocol for its use (13). The authors hypothesized it was predominantly due to the temporarily decrease in the clearance of senescent cells following splenectomy, which results in peripheral leukocytosis. This interesting finding led them to the conclusion that while performing CRS + HIPEC, this could be an additional argument to perform splenectomy.

The effects of splenectomy are well known in the trauma population. It is associated with leukocytosis and thrombocytosis in the postoperative period. The infection rate with encapsulated bacteria is significantly higher if patients are not vaccinated and can put the patient at risk for

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overwhelming post-splenectomy sepsis (OPSI) which has a mortality of up to 70% (14). Thrombosis and cardiovascular complications have also been noted in post splenectomy populations (15). In addition, the spleen plays a role in immunity, which is incompletely understood. It can be difficult to determine the cause of the elevated white blood cells in the postoperative period. Is it only the physiologic inflammatory response to splenectomy or a prodrome to an undetected infection? Toutouzas found that in the trauma population on the fifth operative day, a leukocyte count (WBC) higher than 15 x 10^9/L, a platelet count divided by the WBC less than 20 and a injury Severerity Score higher than 16 was predictive of sepsis 97% of the time (16). In a prospective study, Weng confirmed these findings (17). In the context of an extensive procedure like CRS + HIPEC, patients are at high risk for infectious complications and higher WBC can be seen. Perioperative vaccination to prevent OPSI is also very important. Becher and al. applied a thorough vaccination protocol and had no OPSI during their follow up period.

In the gynecology literature, splenectomy as part of CRS has been investigated. Bidus and al. have shown that post splenectomy patients after CRS had a higher platelet and white blood cell counts than for patients with spleen preservation (18). Leukocytosis alone was not a predictive factor for infection. McCann and al. have described a series of 44 splenectomised patients with CRS for ovarian cancer. They found that splenectomy was an independent factor for worse overall survival (19). They hypothesized that increased extent of disease affected the spleen and was also associated with a worse outcome. Another possible explanation relates to the immune function of the spleen. These hypotheses can also be applied to the present article. Magtibay and al. also studied the effects of splenectomy in CRS for ovarian cancer and found no difference in prognosis nor infectious complications (20). He concluded that splenectomy should be part of the cytoreduction when involved by tumor.

The hematologic effects of systemic MMC are important. Its dose limiting toxicity is myelosuppression particularly thrombocytopenia and leucopenia which can occur following only one dose (21). When given intra-peritoneal, the systemic effects should be lessened (22). However, myelosuppression still exists with HIPEC (23). Sugarbaker reported 28% grade IV hematologic adverse events with HIPEC, predominantly neutropenia (24). A similar effect is seen with oxaliplatin (25). In the present study, 5 patients died from sepsis with cytopenia, which probably contributed to this outcome. Severe or febrile neutropenia is usually treated with G-CSF. This study raised the interesting fact that transient leukocytosis associated with splenectomy might significantly help reduce the need for G-CSF. This finding holds true for the authors as per their protocol for G-CSF administration, which is, to our knowledge, not a standard practice in the various HIPEC-specialized centers nor easily extrapolated from the established guidelines for use of growth factor support (26). Whether it ameliorates the long-term outcome of these patients remains to be proven. The costs of longer hospital stay and increased transfusion rates would overweight any economic advantage of reduced G-CSF usage in the splenectomized population.

Splenectomy in our opinion remains a procedure with non-negligible risks of infection, OPSI, thrombosis, and depressed immune function requiring vaccination optimally prior to its undertaking. Its exact role in immune modulation is yet to be clarified. Splenectomy as part of CRS + HIPEC is, from our point of view, to be performed only if it is affected by disease. The retrospective data herein presented is an important first step in further elucidating information on toxicity of this aggressive procedure that can change the prognosis of eligible patients. Before any firm conclusions on hematologic toxicities can be reached, however, further such reports will be needed applying objective reporting criteria based on conventional practices of a standard of clinical care.

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