Original Article

Splenectomy ameliorates hematologic toxicity of hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is a promising modality for peritoneal carcinomatosis. Splenectomy is frequently required, however effect upon hematotoxicity is unknown.

Methods: 195 patients undergoing the procedure were evaluated and granulocyte colony stimulating factor administered for white blood cell counts <4.0.

Results: 52% of 195 underwent splenectomy; average white blood cell and platelet nadirs were 6.1,172. Non-splenectomy patients averaged white blood cell nadir 4.6, platelet nadir 164.1. Granulocyte colony stimulating factor administered in 29% of splenectomy, 43% of non-splenectomy (P=0.043).

Conclusion: Splenectomy ameliorates hematotoxicity of hyperthermic intraperitoneal chemotherapy and significantly reduces post-operative granulocyte colony stimulating factor requirements.

KEY WORDS peritoneal carcinomatosis, hyperthermic intraperitoneal chemotherapy, splenectomy

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Introduction

Peritoneal dissemination or carcinomatosis is a terminal disease and is one of the most common routes of spread of abdominal carcinoma (1). Studies demonstrate that is the primary cause of death in patients with resected intra-abdominal carcinomas (2-4). Cytoreductive surgery alone has had limited utility in the treatment of peritoneal carcinomatosis. Treatment of peritoneal carcinomatosis with brachytherapy or external beam radiation therapy has not been efficacious (5). Despite recent advances in systemic chemotherapy, its effect is limited in part by the plasma/peritoneal partition limiting entry of agents into the peritoneum. Thus far, systemic chemotherapy has provided modest improvement in survival for patients with peritoneal carcinomatosis (1,6).

Administration of intraperitoneal chemotherapy after cytoreductive surgery delivers high and persistent local concentrations of the chemotherapeutic agent, while limiting systemic toxicity (7). Mild hyperthermia has been shown to potentiate the effects of chemotherapeutic agents such as cisplatin and mitomycin C, and these interactions are enhanced under hypoxic conditions (8-10). Synergy between hyperthermia and the chemotherapeutic agents occurs independently of the cell cycle, which allows for enhanced tumoricidal activity with brief exposures (11). Mitomycin C is the most commonly administered agent in hyperthermic intraperitoneal chemotherapy, however oxaliplatin has been used as well. These agents are utilized because of a highly favorable ratio between intraperitoneal concentration versus plasma concentration over time (2,12-14). The combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy maximizes the therapeutic benefit and has been shown to improve survival and quality of life in select patients (7,15,16).

The goal of cytoreduction is the resection of all gross tumor, and this can necessitate resection of the peritoneum with multivisceral resections, such as splenectomy. Current morbidity rates range from 27% to 56% at centers which

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perform hyperthermic intraperitoneal chemotherapy (7), and one component of this is hematologic toxicity. Splenectomy results in elevated postoperative cell counts, primarily due to decreased clearance of senescent cells (17). Therefore, we investigated the effect of splenectomy on postoperative hematologic toxicity in a series of 195 patients undergoing hyperthermic intraperitoneal chemotherapy.

Materials and methods

Approval for this retrospective study was obtained from the Internal Review Board at Wake Forest University Medical Center in Winston-Salem, North Carolina. We studied a total of 195 patients with peritoneal carcinomatosis, who underwent initial cytoreductive surgery followed immediately by hyperthermic intraperitoneal chemotherapy, between December 2003 and December 2007, at our tertiary care institution. All patients were evaluated in the surgical oncology clinics preoperatively and had pathologic confirmation of peritoneal carcinomatosis prior to the procedure.

Cytoreductive surgery

Cytoreductive surgery was performed with the goal of the removal of all gross tumor and involved organs, peritoneum, or tissue deemed technically feasible and safe for the patient. Any tumors adherent or invasive to vital structures that could not be removed were cytoreduced using the cavitational ultrasonic surgical aspirator (CUSA; Valleylab, Boulder, Colo.). Peritonectomy procedures were performed as indicated. The resection status of patients was judged after cytoreductive surgery using the following classification: R0-complete removal of all visible tumor and negative cytologic findings or microscopic margins; R1-complete removal of all visible tumor and positive post-perfusion cytologic findings or microscopic margins; R2a-minimal residual tumor, nodule(s) measuring 0.5 cm or less; R2b-gross residual tumor, nodule greater than 0.5 cm but less than or equal to 2 cm; and R2c-extensive disease remaining, nodules greater than 2 cm. Splenectomy was performed when gross disease was found on the capsule of the spleen, indicating a higher burden of peritoneal dissemination requiring more extensive surgery.

Hyperthermic intraperitoneal chemotherapy

Patients were passively cooled to a core temperature of approximately 34°C to 35°C by passive measure (i.e., not warming airway gases or intravenous solutions and cooling the room). After cytoreductive surgery was completed, peritoneal perfusion inflow and outflow catheters were placed percutaneously into the abdominal cavity. Temperature probes were placed on the inflow and outflow catheters. The abdominal skin incision was closed temporarily with a running cutaneous suture to prevent leakage of peritoneal perfusate. A perfusion circuit was established with approximately 3 L of Ringer's lactate. Flow rates of approximately 800 to 1000 mL/min were maintained using a roller pump managed by the pump technician. The circuit continued through a pump, then a heat exchanger and then back to the patient.

Constant temperature monitoring was performed at all temperature probes. Once inflow temperature exceeded 38.5°C, 30 mg of mitomycin C was added to the perfusate. At 60 minutes an additional 10 mg of mitomycin C was added to keep mitomycin C perfusate concentrations higher than 5μg/mL. A maximum inflow temperature of 42.0°C was realized during perfusion, with a target outflow temperature at the pelvis of 40°C. The abdomen was gently massaged throughout perfusion to improve drug distribution to all peritoneal surfaces. Total planned perfusion time after the initial addition of mitomycin C was 120 minutes. In certain patients (elderly individuals, those with extensive previous chemotherapy, those with inanition or poor performance status, and patients having extensive peritoneal stripping during surgery), reductions in the dose of mitomycin C (to 30 mg total) or perfusion time (to 60-90 minutes) were made due to concerns about potential toxic effects. Oxaliplatin was administered to a total of 21 of the 195 patients (11%) at a dose of 200 mg/m^2 for a total of 120 minutes; no similar reductions in dosage were needed for oxaliplatin patients (18).

Postoperatively, patients had complete blood counts determined daily until discharge. Treatment with recombinant granulocyte colony stimulating factor (Neupogen) at a dose of 5μg/kg/day was initiated when their white blood cell counts were <4,000/mm. The granulocyte colony stimulating factor was continued until the white blood cell was >10,000/mm, a value in the normal range for our laboratory (19). Hematologic toxicity was graded on a standard scale from 0-5, with 5 being most severe using the National Cancer Institute's Common Terminology Criteria for Adverse Events standard criteria (20).

Results

One hundred ninety five patients (101 women, 94 men), aged 25 to 81 years (mean 53), with peritoneal carcinomatosis underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. The primary site of origin of the peritoneal carcinomatosis and R resection status are shown in Table 1. There were 101 patients (52%) who underwent a splenectomy during

Table 1 Tumor characteristics by splenectomy group

Tumor characteristic	Patients (n=195)	Splenectomy (n=101)	Non-splenectomy (n=94)
Site of origin			
Adrenal	1	1	0
Appendix	120	69	51
Colon	43	17	26
Gastric	5	1	4
GIST	2	0	2
Mesothelioma	4	3	1
Ovary	5	3	2
Pancreas	1	0	1
Rectal	3	2	1
Sarcoma	3	3	0
Small Bowel	3	0	3
Unknown	5	2	3
R Status			
R0/R1	95	33	62
R2a	51	38	13
R2b	34	22	12
R2c	15	8	7

cytoreductive surgery. Splenectomy rates were significantly different by R resection status ($P<0.0001$), with 33 splenectomies in the 95 R0/R1 resections (35%), 38 splenectomies in the 51 R2a resections (75%), 22 in the 34 R2b resections (65%), and 8 in the 15 R2c resections (53%). Overall, 6 of 101 patients (6%) in the splenectomy group and 3 of 94 patients (3%) in the non-splenectomy group died within 30 days of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (not statistically different). Cytopenia contributed to death from sepsis in 4 patients (4%) in the splenectomy group and 1 patient (1%) in the non-splenectomy group (not statistically different).

The average hospital stay was significantly different ($P=0.001$) between the two groups, with the splenectomy group average being 20 days (median 11 days) and the average stay for the non-splenectomy group being 12 days (median 9 days).

Dose reduction of mitomycin C was required in 2 patients in the non-splenectomy group and 2 patients in the splenectomy group. For patients in the splenectomy group, the average white blood cell nadir was 6.1 +/- 3.4 (range 0.3 to 14.7) on day 7.2. The average absolute neutrophil count was 5.2 +/- 3.6 (range 0.1 to 13.4), the average platelet nadir was 172.0 +/- 81.9 (range 3.0 to 381.0), and the average hemoglobin nadir was 7.5 +/- 1.0 (range 4.9 to 10.3). For patients in the non-splenectomy group, the average white blood cell nadir was 4.6 +/- 2.4 (range 0.5 to 13.2) on day 6.0. The average absolute neutrophil count was 3.9 +/- 2.7 (range 0.2 to 14.5), the average platelet nadir was 164.1 +/- 73.0 (range 6.0 to 426.0), and the average hemoglobin nadir was 8.2 +/- 1.8 (range 4.4 to 13.9).

Hematologic toxicity grade by National Cancer Institute criteria is shown for white blood cell, platelets, and hemoglobin in Table 2. White blood cell toxicity was significantly lower in the splenectomy group compared to the non-splenectomy group ($P=0.048$). Platelet toxicity was not statistically significantly different between the two groups ($P=0.24$). Hemoglobin toxicity was significantly worse in the splenectomy group ($P=0.003$). There was no statistically significant difference in hematologic toxicity between those receiving mytomycin C and those receiving oxaliplatin ($P=0.754$).

Granulocyte colony stimulating factor was administered in 29% of splenectomy patients versus 43% of non-splenectomy patients ($P=0.043$). Granulocyte colony stimulating factor was administered for an average of 2.9 +/- 2.1 days (range 1.0 to 8.0) in the splenectomy group, versus an average of 3.3 +/- 3.3 days (range 1.0 to 18.0) in the non-splenectomy group. The difference in the average number of days treated with granulocyte colony stimulating factor was not statistically significant ($P=0.61$).

During the post-operative period, there were significant differences in the number of red blood cell transfusions required for the splenectomy group compared to the

Table 2 Hematotoxicity by splenectomy group

NCI Grade	Splenectomy group	Non-splenectomy group	Total
White Blood Cell Toxicity			
0	58 (57%)	35 (37%)	93
1	26 (26%)	41 (44%)	67
2	6 (6%)	5 (5%)	11
3	6 (6%)	9 (10%)	15
4	5 (5%)	4 (4%)	9
5	0 (0%)	0 (0%)	0
Total	101 (100%)	94 (100%)	195
Platelet Toxicity			
0	59 (58%)	52 (56%)	111
1	30 (30%)	34 (36%)	64
2	3 (3%)	3 (3%)	6
3	0 (0%)	2 (2%)	2
4	9 (9%)	3 (3%)	12
5	0 (0%)	0 (0.0%)	0
Total	101 (100%)	94 (100%)	195
Hemoglobin Toxicity			
0	2 (2%)	1 (1%)	3
1	3 (3%)	18 (19%)	21
2	26 (26%)	26 (28%)	52
3	55 (54%)	34 (36%)	89
4	15 (15%)	15 (16%)	30
5	0 (0%)	0 (0%)	0
Total	101 (100%)	94 (100%)	195

The toxicities of patients in the splenectomy and non-splenectomy groups based on the National Cancer Institute grading criteria for white blood cell (P=0.048), platelets (P=0.24), and hemoglobin (P=0.003). NCI=National Cancer Institute.

non-splenectomy group (Table 3). Over the first 10 post-operative days, there was an average of 3.6 +/- 3.8 red blood cell transfusions (median 2.0; range 0.0 to 19.0) in patients in the splenectomy group versus 2.1 +/- 3.0 red blood cell transfusions (median 1.0; range 0.0 to 13.0) in the non-splenectomy group (P=0.004). A total of 70 (69%) splenectomy patients and 48 (51%) non-splenectomy patients got red blood cell transfusions over the first 10 days. Over the entire hospitalization, there was an average of 6.9 +/- 14.9 red blood cell transfusions (median 3.0; range 0.0 to 123.0) in patients in the splenectomy group versus 2.7 +/- 4.2 red blood cell transfusions (median 0.5; range 0.0 to 25.0) in the non-splenectomy group (P=0.009). A total of 72 (71%) splenectomy patients and 48 (51%) non-splenectomy patients got red blood cell transfusions over the entire hospitalization.

The difference in plasma transfusions post-operatively was statistically significant between the two populations (Table 3). Over the first 10 post-operative days, there was an average of 0.9 +/- 2.4 plasma transfusions (median 0.0; range 0.0 to 13.0) in patients in the splenectomy group versus 0.2 +/- 1.1 platelet transfusions (median 0.0; range 0.0 to 6.0) in the non-splenectomy group (P=0.012). A total of 19 (19%) splenectomy patients and 5 (5%) non-splenectomy patients got plasma transfusions over the first ten days. Over the entire hospitalization, there was an average of 1.3 +/- 3.7 transfusions (median 0.0; range 0.0 to 27.0) in patients in the splenectomy group versus 0.3 +/- 1.2 platelet transfusions (median 0.0; range 0.0 to 7.0) in the non-splenectomy group (P=0.008). A total of 22 (22%) splenectomy patients and 6 (6%) non-splenectomy patients got plasma transfusions over the entire hospitalization.

There was no significant difference in the number of platelet transfusions between the splenectomy and non-splenectomy groups at 10 days post-operatively (P=0.10), 30 days post-operatively (P=0.45), or during the total

Table 3 Blood product utilization by splenectomy group

Product transfused	Splenectomy group (n=101)				Non-Splenectomy group (n=94)				*P*-value
	Mean	Median	SD	No. Pts	Mean	Median	SD	No. Pts	
RBC									
# units at 10 days	3.6	2.0	3.8	70 (69%)	2.1	1.0	3.0	48 (51%)	0.004
# units at 30 days	5.4	3.0	11.2	72 (71%)	2.5	1.5	3.6	48 (51%)	0.020
Total hospitalization	6.9	3.0	14.9	72 (71%)	2.7	0.5	4.2	48 (51%)	0.009
Plasma									
# units at 10 days	0.9	0.0	2.4	19 (19%)	0.2	0.0	1.1	5 (5%)	0.012
# units at 30 days	1.1	0.0	3.0	20 (20%)	0.3	0.0	1.2	6 (6%)	0.018
Total hospitalization	1.3	0.0	3.7	22 (22%)	0.3	0.0	1.2	6 (6%)	0.008
Platelets									
# units at 10 days	0.3	0.0	1.1	13 (13%)	0.1	0.0	0.7	3 (3%)	0.100
# units at 30 days	0.9	0.0	4.3	14 (14%)	0.4	0.0	3.2	3 (3%)	0.450
Total hospitalization	1.8	0.0	8.5	15 (15%)	0.5	0.0	3.5	3 (3%)	0.180

Differences in post-operative blood products utilization between the splenectomy and non-splenectomy populations. RBC=Red Blood Cells; No. Pts=number patients transfused; SD=Standard Deviation.

hospitalization (P=0.18) (Table 3). The difference in cryoprecipitate transfusions was not significant.

Discussion

Utilizing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy together is a promising modality for the treatment of patients with a variety of peritoneal surface malignancies. However, the morbidity and mortality of hyperthermic intraperitoneal chemotherapy are significant, principally due to the extent of surgery necessary for optimal cytoreduction (21). The rates of morbidity range from 27 to 56% at various centers that perform hyperthermic intraperitoneal chemotherapy, and are thought to be related to the extent of carcinomatosis, duration of the operation, preoperative performance status of the patient, and the number of anastomoses (7,22). The most common complications are abscess, fistula, prolonged ileus, pneumonia and hematologic toxicity (7,23).

Splenectomy is well known to result in postoperative leukocytosis and thrombocytosis (17,24); this increase in the white blood cell and platelet counts have previously been shown to occur after cytoreductive surgery without hyperthermic intraperitoneal chemotherapy for carcinomatosis (17). In patients undergoing cytoreductive surgery together with hyperthermic intraperitoneal chemotherapy, only one previous study which we are aware of assessed the relationship between splenectomy and postoperative neutropenia; no association was found (25). Therefore, we chose to examine the effect of splenectomy on hematologic toxicity after hyperthermic intraperitoneal chemotherapy with cytoreductive surgery, and assess the use of granulocyte colony stimulating factor.

In the patients who underwent splenectomy, the white cell nadir was higher, and therefore, splenectomy ameliorated the neutropenia attendant to hyperthermic intraperitoneal chemotherapy. This resulted in a significant decrease in the need for recombinant granulocyte colony stimulating factor support using a standard protocol for its utilization. The platelet nadir was also higher in the splenectomy group, though this did not result in a significant difference in platelet utilization.

Since patients who underwent splenectomy in this experience had disease seen grossly on the organs, splenectomy also correlates with increased tumor burden. Consequently, it is not surprising that a significantly higher grade hemoglobin toxicity was seen in the splenectomy cohort as they required a more extensive operative intervention. This is consistent with the lower hemoglobin nadir in the splenectomy group, and translated into significantly more red blood cell transfusions in this population.

Furthermore, given the increased peritoneal dissemination in splenectomy patients compared to non-splenectomy patients, and thus the need for more extensive multivisceral resection, it is also not surprising that the splenectomy cohort had, on average, a significantly longer hospital stay. Additionally, while a higher proportion of splenectomy patients expired, there was not a statistically significant difference in the mortality between the two

groups or in the proportion of patients who expired from cytopenia.

Splenectomy is associated with morbidities including atelectasis, pleural effusion, pancreatic injury, thrombocytosis, subphrenic abscess, and pancreatic pseudocyst formation (26). A feared complication after splenectomy is overwhelming sepsis, which has an overall mortality of 50%, and may occur between 24 days to 65 days after surgery (27). Pneumococcus is the causative organism in over 60% of cases. Our current standard of care involves vaccination with polyvalent pneumococcal vaccine, H. influenzae type b conjugate, and meningococcal polysaccharide vaccine within 2 weeks of splenectomy (28). We routinely administer, and suggest vaccinations for patients undergoing splenectomy. When splenectomy can be anticipated based upon imaging, preoperative vaccination is preferred. Utilizing this vaccination protocol, we have not encountered a case of overwhelming post-splenectomy sepsis in this patient group to date.

We acknowledge that our study has limitations. First, our conclusions are drawn from a limited sample size of 195 patients. Concomitantly, in addition to the specific differences between the splenectomy and non-splenectomy patient populations described, other factors may have contributed to our conclusions. Furthermore, due to the low number of patients receiving only oxaliplatin (n=21) we caution making definitive conclusions from a subanalysis of patients receiving only mytomycin C and only oxaliplatin. Lastly, this study is a retrospective analysis, and therefore is prone to the potential limitations and biases therein.

Conclusion

Splenectomy ameliorates the hematologic toxicity attendant to hyperthermic intraperitoneal chemotherapy. Further, it significantly reduces the number of patients who require post-operative growth factor support. To our knowledge, this is the first report of this finding. While we do not suggest routine splenectomy as part of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, this effect of amelioration of hematologic toxicity should be considered when contemplating splenectomy during cytoreductive procedures prior to chemoperfusion.

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