Morbidity and Mortality of Early Postoperative Intraperitoneal Chemotherapy as Adjuvant Therapy for Gastric Cancer

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Intraperitoneal chemotherapy (IC) is emerging as a valuable adjuvant therapeutic modality in patients with gastric cancer. The purpose of this study was to assess morbidity and mortality of early postoperative IC (EPIC) in gastric cancer patients. Two hundred forty-eight gastric cancer patients thought to have resectable cancer were randomized intraoperatively to receive EPIC with mitomycin C on postoperative day 1 and 5-fluorouracil on postoperative days 2 to 5 versus surgery only. Sixty-four patients who were stage IV at histopathologic examination remain in the analysis. Morbidity and mortality were compared using Fisher's exact test. All patients completed the therapy. In the study group, overall morbidity was higher than in the control group (28.8% versus 20.3%, respectively), although the difference was not significant (P = 0.121). Intra-abdominal sepsis without anastomotic leak (P = 0.008) and bleeding (P = 0.002) occurred significantly more often in the study group. Also, 37.6% of patients who received EPIC experienced a variety of minor complications attributable to EPIC. Postoperative mortality was higher in the study group (5.6%) than in controls (0.8%), but not significantly (P = 0.299). Patients treated with EPIC stayed in the hospital an average of 4 days longer (P = 0.002); in patients with morbidity, however, there was no difference with the control group. A period analysis of the morbidity demonstrated that it followed the pattern of a learning curve. Surgery with EPIC tended to increase the postoperative morbidity and mortality. The therapy-associated risk must be justified by a significant improvement in survival of treated patients with stage III disease. Selective application of peroperative IC may be indicated.

There has been no improvement in the survival of patients with resectable gastric cancer treated with surgery alone, adjuvant systemic chemotherapy, and radiotherapy. In contrast, perioperative intraperitoneal chemotherapy (IC) was associated with improved survival in several randomized trials. In another randomized trial, there was a positive survival trend after surgery with IC compared with surgery alone.

One trial of delayed postoperative IC was not associated with appreciable difference in outcome. It seemed from the analysis of the timing of IC administration in these trials that intraoperative or early postoperative (days 1–5) treatments tended to improve long-term results, as opposed to delayed postoperative single-drug therapy. Possible explanations of this phenomenon were reviewed elsewhere.

A body of evidence showing benefits from adjuvant perioperative IC for gastric cancer is growing. Also, concern regarding potential-associated morbidity increases. Indeed, it was reported that IC used even as a single therapeutic modality was associated with an 11 to 30 per cent incidence of infectious peritonitis. In an experimental setting, IC was associated with delayed healing of intestinal anastomosis and wounds.

The following presents the analysis of morbidity and mortality encountered in the prospective randomized controlled trial of early postoperative IC (EPIC) as an adjuvant for patients with resectable gastric cancer.

Patients and Methods

From January 1990 until December 1995, 248 patients with biopsy-proven gastric cancer without distant metastases, according to preoperative routine staging (physical examination, chest X-ray, CT scan, or ultrasound of the abdomen) and intraoperative staging, were enrolled in the study. Only patients thought
to be resected with curative intent were eligible for randomization. Patients were randomized intraoperatively after exploration of the peritoneal cavity to receive early postoperative intraperitoneal mitomycin C 10 mg/m² on postoperative day 1 and 5-fluorouracil 700 mg/m² on days 2 to 5 versus surgery alone. Patients older than 70 years were excluded. Other exclusion criteria were prior antitumor therapy or concurrent malignancy except for basal cell carcinoma of the skin, or carcinoma in situ of the cervix, and pregnancy. All patients were required to have a leukocyte count of ≥4000/mcl, a platelet count of ≥150,000/mcl, a blood urea nitrogen level of <30 mg/Dl, and a creatinine concentration of <1.5 mg/Dl. All patients signed an informed consent explaining the investigational nature of the study. Postoperatively, histological type, tumor-node-metastasis category and stage were assigned using the Fourth Edition of the International Union Against Cancer classification, which corresponds directly to those provided in the manual of the American Joint Committee on Cancer. Morbidity and mortality associated with surgery with EPIC were evaluated in all 125 patients randomized to the study group and compared with that of 123 patients in the control group. All patients in the study group completed the treatment.

Surgery

Depending on location and type of growth, either a total or a distal subtotal gastrectomy was selected. Routine Roux-en-Y reconstruction with stapled esophagojejunostomy or hand-sewn Billroth-II gastrojejunostomy were used. All patients underwent extended lymphadenectomy with removal of N1-2 nodes (D2) in about one-third, and N1-3/L-4 nodes (D3/4) in two-thirds of the cases (D-dissection of the lymph nodes according to Japanese Classification of Gastric Carcinoma). The extent of the lymph node dissection was selected at the discretion of the surgeon, depending on the anticipated stage. In patients randomized to receive EPIC, a Tenckhoff catheter and two closed-suction drains were placed into the peritoneal cavity before closure.

EPIC

On the day of the surgery, the peritoneal cavity was irrigated with 1.5 per cent dextrose dialysis solution until drainage from the catheters became clear. On the 1st postoperative day, 1 liter of 1.5 per cent dextrose dialysis solution containing 10 mg/m² of mitomycin C warmed to 37°C in a dry incubator was instilled as rapidly as possible into the peritoneal cavity via a Tenckhoff catheter, and all drains remained clamped for 23 hours. During treatment with mitomycin C, a urine output of >1 mL/kg body weight/hour was maintained. On days 2 to 5 the peritoneal cavity was drained for 1 hour through all catheters, and 700 mg/m² of 5-fluorouracil and 50 mEq of sodium bicarbonate in 1 liter of 1.5 per cent dextrose dialysis solution were instilled daily. Initially, all drains were removed on the 6th postoperative day. But later in the course of the study, they were left in place until drainage subsided.

Statistical Analysis

The analysis comprises all randomized patients, including 64 who had stage IV disease after histopathologic study. Groups of patients with a given characteristic were compared by Fisher’s exact test. Differences in the means of continuous measurements were tested by Student’s t test. The differences were recognized as significant if a P value was <0.05.

Results

There were 125 patients in the study group and 123 patients in the control group. Groups were comparable according to all clinical and pathological parameters, except for the duration of stay in the hospital. Even though the protocol required resectable gastric cancer, 64 patients upon histopathologic examination had stage IV disease.

Overall Morbidity

After surgery with EPIC, 28.8 per cent of patients experienced postoperative complications versus 20.3 per cent in the control group (Table 1). Overall, the difference was not significant. There was no difference in the incidence of anastomotic leaks. Contrary to that, there was a statistically significant increase in the incidence of intra-abdominal sepsis with abscess formation or peritonitis without anastomotic leak. Also, there was a statistically significant increase in the incidence of intra-abdominal bleeding. Most of the cases were managed with conservative measures so that the incidence of relaparotomy and percutaneous drainage of collections was statistically not different between the groups. The incidence of other complications was comparable between the groups. Though mean duration of stay in the hospital was longer in the study group, in the subgroup of patients with complications there was no such difference.

Mortality

Six patients in the study group and one patient in the control group died of postoperative complications within 30 postoperative days (not significant; P = 0.102). Among the causes of death in the study group
Table 1. Morbidity and Mortality after Surgery with EPIC versus Surgery Alone

<table>
<thead>
<tr>
<th>Morbidity/Mortality</th>
<th>EPIC + Surgery (%)</th>
<th>Surgery only (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>125</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Number of patients with complications</td>
<td>36 (28.8)*</td>
<td>25 (20.3)</td>
<td>0.121</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>4 (3.2)</td>
<td>3 (2.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Intra-abdominal sepsis</td>
<td>17 (13.6)</td>
<td>5 (4.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>Bleeding</td>
<td>12 (9.6)</td>
<td>1 (0.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Chyle leak</td>
<td>2 (1.6)</td>
<td>0</td>
<td>0.498</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>3 (2.4)</td>
<td>0</td>
<td>0.247</td>
</tr>
<tr>
<td>Wound infection</td>
<td>4 (3.2)</td>
<td>5 (4.1)</td>
<td>0.748</td>
</tr>
<tr>
<td>Extra-abdominal complications</td>
<td>6 (4.8)</td>
<td>11 (8.9)</td>
<td>0.197</td>
</tr>
<tr>
<td>Relaparotomy</td>
<td>4 (3.2)</td>
<td>2 (1.6)</td>
<td>0.42</td>
</tr>
<tr>
<td>Percutaneous drainage</td>
<td>7 (5.6)</td>
<td>8 (6.5)</td>
<td>0.765</td>
</tr>
<tr>
<td>Mortality</td>
<td>8 (6.4)</td>
<td>1 (0.8)</td>
<td>0.102</td>
</tr>
<tr>
<td>Mean + SD days in hospital:</td>
<td>19.6 + 11.1</td>
<td>15.4 + 9.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Patients without complications</td>
<td>17.1 + 6.4</td>
<td>13.2 + 5.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with complications</td>
<td>25.1 + 16.3</td>
<td>24.0 + 15.3</td>
<td>0.783</td>
</tr>
</tbody>
</table>

* Morbidity associated with intraperitoneal chemotherapy, per se, is not included.

were anastomotic leak,2 intra-abdominal sepsis without leak,3 and disseminated intravascular coagulation syndrome.4 Another patient died on postoperative day 42 from multiple organ failure after a cerebrovascular accident. After surgery alone, there was one death from anastomotic leak.

Morbidity Attributed to EPIC

A number of postoperative complications were unique for IC (Table 2). They required a prolonged stay in the hospital compared with the time required after surgery alone (17.1 days versus 13.2 days, respectively; P = 0.002, patients without surgical morbidity). Low-grade transient leukopenia occurred in 2.4 per cent of patients. One in three patients experienced prolonged mild-to-moderate abdominal pain, 7.2 per cent experienced prolonged fluid discharge from drains, and 1.6 per cent experienced prolonged ileus.

Morbidity Trends in the Study Group

When analyzed by the initial (1990–1991) and subsequent (1992–1995) periods of the study, the morbidity demonstrated the pattern of a learning curve and decreased in the second period by more than one-half. Nevertheless, the incidence of two types of complications (intra-abdominal sepsis without anastomotic leak and intra-abdominal bleeding) remained stable. Mortality rate also did not change significantly (Table 3).

Discussion

Survival of patients with gastric cancer undergoing presumably curative resection is far from satisfactory, and some researchers suggested lack of progress with the treatment of this malignancy in recent decades.5 Apart from continuing discussion about validity of extended lymphadenectomy, not much attention has been devoted to new therapeutic options. Peritoneal dissemination remains one of the major sites of recurrence after curative resection for gastric cancer, in spite of adjuvant treatments.22,23

Accumulation of knowledge about physiology of peritoneal-plasma barrier and pharmacokinetics of IC resulted in several randomized and case-controlled trials of adjuvant IC for resectable gastric cancer.5,10,24–26 In all of them except one,10 survival tended to be higher after surgery with IC, although statistically significant improvement in overall survival was reached in only two studies.5,25 In another three trials, survival advantage after surgery with hyperthermic intraoperative IC was demonstrated in subgroups of patients with serosal invasion (T3–4 tumors)5 and a number of metastatic lymph nodes between 1 and 9,7 as well as in patients with stage III.8 Data of the former two randomized studies corresponds to the findings of statistically significant improvement in survival of patients with T3–4 and N2 or stage III tumors,8 who constituted about two-thirds of all patients in the third randomized trial of adjuvant IC.

Hence, it can be concluded that IC is a valuable therapeutic modality able to improve survival in pa-
Table 3. Pattern of Learning Curve with the Morbidity and Mortality after Surgery with EPIC

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>20 (36.4)</td>
<td>10 (14.3)</td>
<td>30 (24)</td>
<td>0.004</td>
</tr>
<tr>
<td>Leakage around catheter</td>
<td>12 (21.8)</td>
<td>2 (2.9)</td>
<td>14 (11.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prolonged drainage</td>
<td>2 (3.6)</td>
<td>7 (10)</td>
<td>9 (7.2)</td>
<td>0.296</td>
</tr>
<tr>
<td>Prolonged ileus (&gt;7 days)</td>
<td>1 (1.8)</td>
<td>1 (1.4)</td>
<td>2 (1.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (1.8)</td>
<td>2 (2.9)</td>
<td>3 (2.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Catheter problems</td>
<td>1 (1.8)</td>
<td>0</td>
<td>1 (0.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>Bleeding</td>
<td>10 (18.2)</td>
<td>2 (2.9)</td>
<td>12 (9.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Intra-abdominal sepsis</td>
<td>8 (14.6)</td>
<td>9 (12.9)</td>
<td>17 (13.6)</td>
<td>0.785</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>2 (3.6)</td>
<td>2 (2.9)</td>
<td>4 (3.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>All EPIC-related morbidity</td>
<td>29 (52.7)</td>
<td>16 (22.9)</td>
<td>47 (37.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (5.4)</td>
<td>5 (4.3)</td>
<td>8 (6.4)</td>
<td>0.299</td>
</tr>
<tr>
<td>Percentage of patients treated this period</td>
<td>55 (44)</td>
<td>70 (56)</td>
<td>125 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Patients with resectable gastric cancer stage III, serosal invasion (T3–4 category), and limited lymph node metastases. Effectiveness of adjuvant IC may be directly related to a methodology and timing of its administration.12 All positive randomized trials used intraoperative or early postoperative timing of chemotherapy delivery. Therefore, perioperative administration of adjuvant treatment is of definite importance for the outcome.

Incorporation of perioperative IC into a treatment strategy may be stalled by the surgeon’s fear of increased morbidity and mortality. Results of this study showed that caution is necessary in the implementation of these treatments. Overall morbidity and mortality were not statistically different between the study and control groups, and these data correspond to the results of previous trials.5,9,28 Similar good tolerability and low morbidity were reported in two randomized trials of adjuvant EPIC with 5-fluorouracil for colorectal cancer.27,28 Contrary to our results in these studies, there was no statistically significant increase in the incidence of intra-abdominal sepsis without leak and bleeding. It can be suggested that a more extensive resection such as gastrectomy with extended lymphadenectomy is responsible for increased morbidity in this study.

Understandably, early peritoneal lavage depletes local clotting factors and intraperitoneally administered cytostatics depress local immunity, thus creating a milieu for potential morbidity. Meagerous attention to hemostasis, use of drains and aseptic methods of their management, as well as longer stay of drains in place, can decrease the rate of such complications. Approximately one-third of patients in this study experienced peritoneal irritation; this was not as pronounced as in other reported series.29 Taken together, these effects of IC create a different postoperative course to which general surgeons are not accustomed. In the present study, morbidity of perioperative IC followed the pattern of the learning curve and was reduced to acceptable limits.

Analysis of survival data demonstrated that statistically significant survival advantage is limited to patients with gastric cancer stage III.8 The morbidity associated with this treatment justifies selective indications to adjuvant EPIC. The major selection criteria is invasion of the serosal surface of the stomach and involvement of the regional lymph nodes. Of those two, in the operating room only serosal invasion can be assessed more or less reliably. It is a well-known negative prognosticator.30–32 All in all, 73.8 per cent of all patients enrolled in this study had T3–4 tumors. Basically, special attention has to be paid to the exclusion of T1–2 tumors.

The results of this study confirmed that EPIC, being an effective adjuvant treatment, can be administered with acceptable morbidity and mortality. Its administration requires adjustment in both surgical technique and postoperative management to reduce the rate of possible complications and provide for survival benefit in a significant portion of patients.

Conclusion

In this randomized assessment, surgery with EPIC for resectable gastric cancer was associated with a trend toward increased morbidity and mortality. Complications such as intra-abdominal sepsis without anastomotic leak and bleeding were encountered significantly more often in the study group. Also, about one-third of patients in the study group experienced minor side effects of the treatment, which resulted in a prolonged stay in the hospital (an average of 4 days compared with the control group). At the same time, statistically significant improvement in survival of patients with stage III disease (T3–4 and N2 lesions) makes this treatment modality an attractive option in patients with resectable gastric cancer. Selective ap-
proach with exclusion of patients with T1–2 tumors may be indicated.

REFERENCES