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Series Editor

Management of Gastric Cancer

edited by
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Kluwer Academic Publishers

20. Celiac axis infusion (CAI) chemotherapy for advanced gastric cancer

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Introduction

Long-term prognosis of gastric cancer patients mainly depends on early diagnosis. Patients submitted to surgery in advanced stages III and IV do not have more than a 10% 5-year survival expectancy [4]. Although gastric cancer has been proved to be chemosensitive [2,3,5,7], and the rationale for adjuvant chemotherapy is therefore well established, there are no sufficient data so far to demonstrate any substantial benefit in survival. To date radical surgery for early gastric cancer remains the only therapeutic modality with a significant cure rate. It has been the objective of this pilot study to find out whether increased local drug concentrations, given via the arterial route through the celiac axis, lead to higher local response rates than systemic chemotherapy, and therefore potentially induce backstaging of the loco-regional tumor burden.

Materials and methods

Eleven patients with advanced gastric cancer were entered in the study. Tumor staging, grading, and histology are listed in Table 1. The most outstanding symptoms observed were weight loss, diminished performance status (Table 3) in 10 patients, and dysphagia in eight patients. The oldest patient was 82 years, presenting with invasive local recurrence after prior B II resection. Two additional patients, both also suffering from dysphagia, are not listed in this series. One presented with extensive gastric lymphoma and the other patient had a bulky adenocarcinoma. Both were submitted to second-look surgery.

Intraarterial infusion technique

Eleven of 13 patients with bulky tumor invasion around the celiac axis received intraarterial chemotherapy through angiographically placed celiac axis catheters. The chemotherapeutic schedule was administered in four

P. Sugarbaker (ed), MANAGEMENT OF GASTRIC CANCER. *ISBN 0-7923-1102-7.*

Table 1. Staging and grading of advanced gastric cancer patients (n = 11) submitted to regional chemotherapy

Patient	TNM	Histology	Grading	Lauren
1.	$T_4N_1M_0$	Adenocarcinoma	G2	Intestinal
2.	$T_4N_1M_0$	Adenocarcinoma	G3	Diffuse
3.	$T_4N_3M_1$	Adenocarcinoma	G3	Diffuse
4.	$T_3N_1M_1$	Adenocarcinoma	G2	Intestinal
5.	$T_4N_2M_1$	Signetringcarcinoma	G3	—
6.	$T_4N_3M_1$	Adenocarcinoma	G2	Intestinal
7.	$T_4N_3M_0$	Adenocarcinoma	G2	Intestinal
8.	$T_4N_2M_1$	Adenocarcinoma	G3	Intestinal
9.	$T_2N_2M_0$	Adenocarcinoma	G2	Intestinal
10.	$T_3N_2M_1$	Adenocarcinoma	G2	Intestinal
11.	$T_4N_2M_1$	Signetringcarcinoma	G3	—

Table 2. CAI treatment schedule for advanced gastric cancer

Day	Total dose	Infusion time
day 1	14 mg MMC	60 min
day 2	30 mg ADM	60 min
day 3	1000 mg 5-FU	60 min
day 4	1000 mg 5-FU	60 min

CAI cycles given in 4 weeks intervals. Follow-up controls every 3 months.

Table 3. Quality of life index according to Priestman and Baum before and after two cycles of celiac axis infusion for advanced gastric cancer

Patient	Prior to therapy	After 2 cycles
1.	73	82
2.	53	90
3.	58	70
4.	52	70
5.	28	94
6.	38	60
7.	45	75
8.	37	57
9.	63	73
10.	27	56
11.	27	55

$X = 45.4$; $S = 71.1$.

courses, given in 4-week intervals. Drugs were infused over 60 minutes each on 4 consecutive days, consisting of a modified FAM regimen (Table 2). The angiographic catheters remained in situ for 4 days, throughout the therapeutic cycle, and heparin perfusors (20,000/U/day) were connected during the intervals between daily drug infusions. In 2 of 13 patients during initial laparotomy, while primary tumors were considered nonresectable, a Jet Port Allround Celiac Axis Catheter (PfM, Cologne FRG) was implanted. This surgical technique has been described elsewhere [1].

Follow-up

For the estimation of the therapeutic effect, major attention was drawn to changes in the performance status and survival. The decrease of tumor markers was considered an indicator of response, however, improvement or resolution of symptoms, such as dysphagia, were given more importance. Patients were seen for routine follow-up controls every 3 months.

Results

In the group of 11 patients undergoing no further surgery, the quality-of-life index improved from x = 45.4 prior to therapy to x = 71.1 after two cycles of celiac axis infusion. Four patients reported complete resolution of dysphagia and four had substantial improvement. According to tumor markers (CA 19-9) two patients showed a complete remission. However, this could not be confirmed histologically from endoscopical biopsy in the remaining lesion where PRs were noted. The remaining seven patients had partial remissions, considering histology, markers, and CT scan. The overall response rate in this group was 82%, and the median survival was 13 months (Figure 1). The longest actual survival, seen in the patient with prior B II resection, was 34 months.

The patient treated for gastric lymphoma showed complete resolution of dysphagia after two cycles of CAI. Gastroscopy revealed a shrinkage of the formerly bulky tumor to a small ulcer of 8 mm in diameter. This was excised at the occasion of a second-look staging laparotomy where no positive lymph nodes were found and the ulcer proved to be histologically benign. The patient has been in complete remission for 12 months and is gaining weight at a normal performance status.

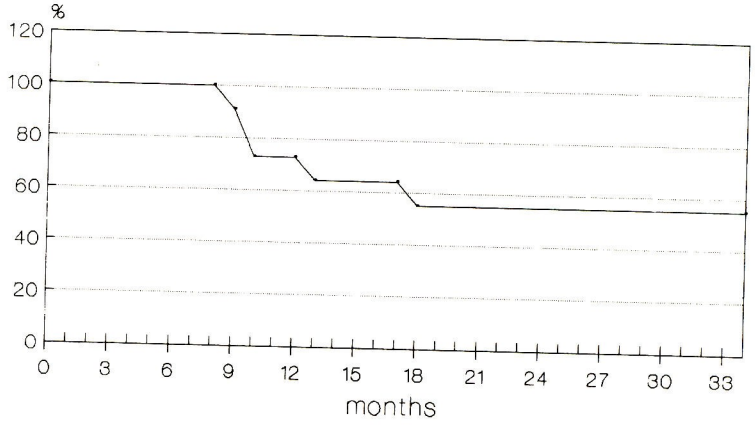

Figure 1. Survival rate after CAI in the treatment of inoperable stomach cancer (n = 11).

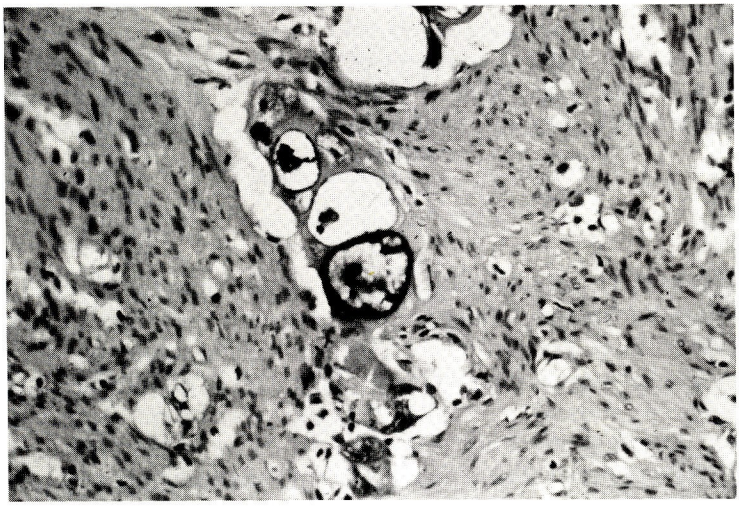

Figure 2. Histology (HE 350X) after two cycles of CAI for gastric adenocarcinoma shows only a few degenerative tumor cells. From R. Bassermann, MD, Insitut f. Pathologie, Kaufbeuren, FRG, with permission.

In the second patient, who had second-look laparotomy and gastrectomy after two cycles, histology showed negative, partially necrotic lymph nodes. An ulcer of 6 cm in diameter with a bulky rim of hard consistency, histologically showed mainly connective tissue and a few tumor cells with extremely degenerative changes (Figure 2). This case was estimated to be a partial remission. The patient has been alive without evidence of disease for 12.5 months.

Side effects

Side effects are usually mild. Some patients, at the most, report mild gastritis. Bone marrow depression was not observed. One patient had chemical cholecystitis during the third and the fourth cycle, without further consequences.

Discussion

In view of an abundant series of reports in the literature indicating that gastric cancer is sensitive to chemotherapy without resulting in a survival benefit,

there was a need to try to improve the local efficacy at the tumor site by means of enhanced drug exposure. F.O. Stephens' data [6] on a 63% 5-year survival in resected gastric cancer patients who had prior regional chemotherapy encouraged us to pursue this concept. It is obvious that the potential of a new treatment modality can best be estimated when rather advanced cases with a poor prognosis are treated firsthand in a pilot trial.

In an attempt to find out whether tumor masses from gastric cancer in the upper abdominal cavity show dose-response behavior when drugs are infused via the tumor-supplying arterial trunc, the celiac axis, we experienced that, in a rather suprising number of cases, improvement or resolution of symptoms such as dysphagia, pain, and weakness was achievable. Eighty-two percent of the patients showed a remarkable response to the treatment, as noted by clinical findings, such as tumor markers, TC scan, and tumor biopsies.

Encouraged by the experiences with our first patients in this series, a second study was initiated where, in not clearly curatively resectable cases, during staging laparotomy a celiac axis port catheter was implanted for subsequent induction chemotherapy, which was done by means of high-dose intraarterial infusion and systemic drug filtration. At the time of the third course, the patients underwent radical gastrectomy with lymphadenectomy. The histological evaluation of the resected specimen clearly revealed the effect of intraarterial induction chemotherapy. One patient out of this series who showed subtotal tumor necrosis has been presented herein. Nevertheless, an answer to the real benefit of cytotoxic celiac axis infusion, with regard to long-term survival, can only be given a couple of years later. Stephens data (6), however, suggest that there might be a coincidence between disease-free intervals and the quality of the initial response. Therefore, in controlled trials, there is a rationale for the impact of high local drug exposure in gastric malignancies with the perspective of tumor downstaging and the aim to regain resectability under simultaneous eradication of lymph node metastases. Beyond all these prospective possibilities, which appear to be worthwhile trying, however, one guideline can already be postulated: Patients can only be cured when tumor lesions are confined to the field of intraarterial high-dose (concentration) therapy, under the exceptional condition that all tumor cells are eradicated. Tumor markers, dependent on tumor mass, thus are not reliable indicators. The only safe procedure consists of a multimodality concept, including subsequent surgical resection and histological verification of the tumoricidal effect of regional chemotherapy.

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