Cancer Immunol Immunother (1982) 13: 182–184

Cancer Immunology Immunotherapy

A Follow-Up Study on Chemoimmunotherapy (5-Fluorouracil and BCG) in Advanced Gastric Cancer

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Summary. *Two hundred and seventeen patients with advanced gastric cancer were classified according to the resectability of the tumour into two groups: I, resectable (non-radical surgery), 99 patients, and II, non-resectable carcinoma, 118 patients. Within each group patients were randomly assigned to receive 5-fluorouracil (5-FU) + BCG, 5-FU, or no further treatment (surgery only). BCG was given by scarification. A 2-year follow-up is reported. The group of patients with resectable tumours and receiving chemoimmunotherapy had a statistically significant prolongation of survival compared with the 5-FU and surgery only groups. No differences in survival were observed between these treatment modalities in patients with non-resectable tumour. These observations indicate that chemoimmunotherapy may be of benefit for a selected group of patients with gastric cancer.*

Introduction

Most gastric cancers are diagnosed late in their course, and hence the majority of patients require palliative or adjuvant chemotherapy. The response rate in patients treated with the commonly used single-agent 5-fluorouracil (5-FU) therapy is about 23%–28% [5], and there is no evidence that any single drug will contribute to survival in these patients [12]. The addition of nitrosoureas and 'lactones' or a combination of both produced no improvement in survival of patients with advanced gastric cancer over that obtained with 5-FU alone [12]. Encouraging results have been observed with a three-drug combination of 5-FU, adriamycin and mitomycin C [11]. A response rate of 42%–55% and significantly longer survival of responders have been noted [2, 14], but overall median survival in gastric cancer has not been significantly improved [14].

It is generally assumed that immunological factors may influence the prognosis of cancer patients, and that non-specific immunostimulation may improve the survival of patients with residual minimal disease [8]. Up to now no comprehensive clinical trial of systemic BCG therapy in gastric cancer has been reported. Torisu et al. [16] have recently shown that patients with advanced gastric cancer treated with BCG, and also other forms of immunostimulation, experienced prolongation of the disease-free interval and survival. Ambus et al. [1] reported that BCG given IP and PO as an adjuvant to chemotherapy with 5-FU increased median survival in patients with residual and recurrent stomach cancer.

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This paper presents a 2-year follow-up of patients with advanced resectable and non-resectable gastric cancer treated with BCG and 5-FU. These observations are a part of the Cracow Medical School Cooperative Trial initiated in 1976, designed for the evaluation of different treatment modalities in gastric cancer. This randomized study was designed to assess the effectiveness of the addition of BCG to 5-FU therapy compared with 5-FU and surgery only. The end-point was the most important and most clearly defined parameter–patient survival [12]. No other attempts were made to assess response to therapy.

Patients and Methods

Patients. Untreated patients with biopsy-proven carcinoma were classified according to the resectability of the tumour into two groups: I, resetable tumour (non-curative resection) with regional lymph node metastases, 99 patients; and II, non-resectable disseminated carcinoma, 118 patients. Patients from group I underwent subtotal resection according to Rydygier, while palliative surgery or laparotomy was performed in group II. Within each group patients were randomly assigned to the following treatment schedules: 5-FU + BCG, 5-FU therapy, surgery only (control). The randomization scheme was 2 : 1 : 2, respectively. Of 21 patients from group I who were randomized to receive 5-FU, five were lost to follow-up. The number of patients, their age and sex, the histology, and numbers of metastatic lymph nodes within the therapeutic groups are presented in Table 1.

Chemoimmunotherapy. Patients were treated with IV infusions of 5-FU (Hoffmann-La Roche) at a dose of 15 mg/kg on days 1–5 and then on days 7, 14, 21, and 28. Chemotherapy started within 4 weeks of surgery.

Fresh-frozen BCG, Moreau strain (Sera and Vaccine Laboratory, Lublin, Poland) was administrated by scarification on the upper arm on an area of 5 cm × 5 cm, according to the technique of Mathé et al. [9]. BCG was applied with a no. 17 needle in a dose of $2-4 \times 10^8$ viable units. BCG was started 7 days after the beginning of chemotherapy. The MD Anderson Hospital protocol for BCG therapy in colorectal carcinoma was followed [10]. BCG was given weekly during the first 3 months, then every second week and continued indefinitely.

Statistical Analysis. The effect of therapy was evaluated in terms of the survival time from admission. Survival rate was calculated by a life-table technique [4]. A generalized

0340-7004/82/0013/0182/$ 01.00

Table 1. Characteristics of patients

Group	Therapy	Number	Age (mean)	M/F ratio	Histological classification according to WHO (%)			Metastatic lymph nodes (%)
					Adeno-carcinoma	Undifferentiated carcinoma	Adenosquamous, squamous and unclassified carcinoma	
I	5-FU + BCG	39	55.9	2.9	66.6	28.2	5.2	57
	5-FU	16	55.0	0.8	68.8	31.2	–	49
	Surgery only	44	60.2	1.4	63.6	31.8	4.5	44
II	5-FU + BCG	43	62.3	2.6	76.7	16.3	7.0	–
	5-FU	26	57.7	2.0	76.9	23.1	–	–
	Surgery only	49	60.1	2.6	73.4	22.4	4.1	–

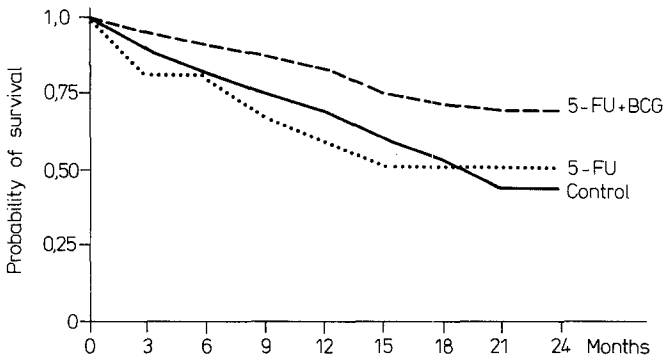

Fig. 1. Survival curves of patients with resectable gastric cancer (group I)

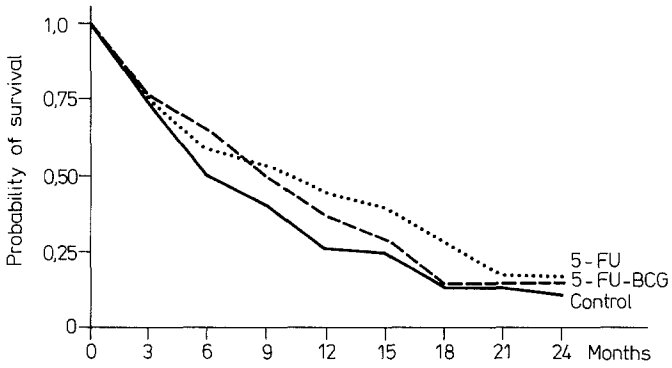

Fig. 2. Survival curves of patients with unresectable gastric cancer (group II)

one-tailed Wilcoxon test was used to assess the differences between the groups [3].

Results

In a pilot study, a group of patients with inoperable metastatic gastric carcinoma who were receiving palliative treatment were given BCG. Since this therapy was well tolerated and at least a subjective improvement was observed in some patients a randomized trial was commenced, and this is reported below.

Patients with advanced resectable cancer, with regional but not distant metastases, were given either BCG and 5-FU (39 patients) or 5-FU alone (16 patients). Their survival rate was compared with that of the surgery only group (44 patients). Figure 1 shows that the chemoimmunotherapy group had an increased survival rate over a period of 24 months compared with both the chemotherapy group and the surgery only group. The difference was statistically significant ($P < 0.005$). There was no significant difference between the 5-FU and surgery only groups.

Group II (unresectable disseminated carcinoma) consisted of 43 patients treated with BCG + 5-FU, 26 patients receiving 5-FU, and 49 patients treated by surgery only. There was no difference in the survival rates between the sub-groups (Fig. 2).

The BCG therapy was well tolerated and no major complications were noted. Systemic reactions were mainly 'flu-like' symptoms with moderate chills and temperature. Local reactions sometimes lasted 2–3 weeks but any discrete scars left usually disappeared completely within a few months. The majority of patients complained of pruritus. In three cases the local skin reactions were very strong and required topical application of steroids and withdrawal of BCG for 4–6 weeks. In these patients the next dose of BCG was halved. In no case did the complications lead to discontinuation of the therapy.

Discussion

The present study demonstrates a prolongation of the survival of patients with resectable advanced stomach carcinoma (group I) treated with BCG in combination with standard 5-FU therapy. The survival of patients receiving 5-FU therapy was comparable to that of the control (surgery only) group. BCG therapy seemed to be of no definite value for patients with non-resectable tumour (group II). However, the validity of this conclusion needs to be confirmed in a larger group.

The recent results of the Japanese trial [16] have indicated that BCG treatment prolongs the disease-free interval and the survival of patients with advanced gastric cancer. It is difficult to compare these findings directly with the present observations, as patients with resectable tumours were assessed together with patients having inoperable tumours, BCG was given intradermally, and other immunostimulant were also used. Our results have to be interpreted with caution because of the small number of patients in each treatment group and because the trial is not yet completed. Furthermore, the effectiveness of BCG therapy alone cannot be assessed. However, there is clear evidence for the benefit of immunotherapy in different forms of malignancy, which has been reviewed by Mathé [8] and Morton and Goodnight [13]. Edynak et al. [6] reported that all ten of their high-risk patients

with gastric cancer who were given BCG and irradiated tumour cells were alive at 1 year, while four of ten control patients had died. Ishikawa et al. [7] have described six long-term survivors with advanced stomach cancer receiving specific immunotherapy. Our results are compatible with those of Ambus et al. [1], who found that patients with resectable and non-resectable gastrointestinal cancer treated with oral BCG and 5-FU tended to survive for a longer period than those receiving 5-FU only. Although the differences in their study were statistically non-significant, the median survival for the BCG group was 48 weeks, as against 24 weeks for the 5-FU group.

Since BCG therapy appears to be well tolerated [cf. 15] and there is no evidence that it leads to enhancement of human tumours [17], it can be suggested as adjuvant treatment for patients with resectable stomach cancer.

Acknowledgements. We wish to express our appreciation to all colleagues who participated in the trial, and in particular to Drs A. Czupryna, J. Kulig, H. Łabza, and J. Panek.

This work was supported by the National Cancer Programme (grant PR-6).

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Received December 8, 1981/Accepted April 6, 1982