Adjuvant Chemotherapy in Gastric Cancer

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The results of adjuvant chemotherapy trials in gastric cancer are less favorable in European and Anglo-American countries than in Japan. The majority of findings in Western countries leads to the conclusion that the routine application of adjuvant chemotherapy for gastric cancer cannot be recommended. The therapeutic benefit reported in Japanese studies is possibly due to the fact that chemotherapy is started intraoperatively or during the immediate postoperative period in Japan as opposed to the procedure in the majority of Western countries. The effectiveness of adjuvant chemotherapy may be improved by intraperitoneal drug administration because peritoneal seedings and lymph node metastases are the major cause of treatment failure after curative gastric cancer surgery. Since the efficacy of adjuvant chemotherapy is influenced by the responsiveness of cancer cells to cytotoxic agents, preoperative chemotherapy could improve the selection of patients for subsequent postoperative adjuvant treatment trials in the future.

A new era of tumor therapy seemed to be dawning when, in the seventies, the promising clinical reports on the efficacy of adjuvant chemotherapy of breast carcinoma were published [1, 2]. The evidence provided seemed to be that the stage of minimal residual disease could effectively be treated by adjuvant chemotherapy, as already indicated by the basic research results obtained with adjuvant chemotherapy in animal experiments [3, 4]. Ten years after the initial euphoria [5] the recent judgment is much more critical. Nevertheless, there is increasing support for the opinion that malignant tumors of seemingly local growth often represent a general disease. These considerations are of utmost importance for surgical adjuvant therapy in gastric cancer, since, for example, microscopically free cancer cells are often detectable in the peritoneal cavity even in the early stage of the disease [6]. Keeping this in mind, following is an analysis of the impact of adjuvant cytostatic treatment comparing published data in the literature and our own experience with this kind of treatment in gastric cancer surgery.

Our Experience

This randomized study of patients with gastric cancer was started in December, 1979. A preliminary report and the 5-year analysis were published previously [7, 8]. One hundred three patients were randomized for the study. Eligibility criteria were: histologically proven gastric adenocarcinoma, which was resected curatively; age under 68 years; no clinically demonstrable or suspected metastases; no presence of a second tumor; no clinical condition predisposing to severe side effects; no previous cytostatic chemotherapy; and patients' consent after information. Eligible patients were stratified according to UICC classifications into stage II (stratum A) and stage III (stratum B) and randomly allocated to the adjuvant chemotherapy or control group. Table 1 shows relevant characteristics of the study groups.

Adjuvant chemotherapy consisted of 8 courses of 5-fluorouracil (5-FU) (10 mg/kg per day x 5) and BCNU (40 mg/m² per day x 5), repeated every 6 to 8 weeks. The first cycle of chemotherapy was administered between days 42 and 46 postoperatively. All patients were evaluated with clinical and laboratory techniques every 8 weeks for the first 18 months and every 3 months thereafter. Chest x-ray, abdominal sonography, and gastroscopy were performed every 6 months. Recurrence was documented on x-ray, computed tomography (CT) scan, and endoscopy with biopsy or cytology, if possible. All patients were followed until death. Endpoints of the study were the time of relapse and the time of death. Toxicity of chemotherapy was recorded utilizing the WHO scale. Probability of disease-free survival and of survival was calculated according to Kaplan and Meier; the curves were analyzed for difference in survival using the log-rank test [9].

The present analysis was performed in March, 1986, and includes patients' follow-up until December, 1985. During this observation period a total of 49 recurrences occurred, 28 in the control and 21 in the chemotherapy group. There was no difference in type and localization of the recurrences between the groups (Table 2). Actuarial survival curves for disease-free and overall survival rate are depicted in Figs. 1 and 2. There is no statistically significant difference, when the whole group or the strata are compared.

On the other hand, all patients experienced mild (WHO grade 1) gastrointestinal toxicity including nausea and transient anorexia. These symptoms tended to become more severe during the course of therapy. Grade 2–3 gastrointestinal toxicity was observed in 28 of 42 patients and hematotoxicity grade 2–3 in 4 of 42 patients; in 17 of 42 patients the projected dose had to be modified because of intolerance. Extensive hematological studies, which were reported in detail earlier, indicate that there is
only an incomplete recovery of granulopoiesis with persistent severe depression of granulopoietic precursor cells (CFU-c) in peripheral blood and bone marrow [10]. A comparison of the recurrence-free interval or survival rate within the chemotherapy group with regard to complete or modified treatment showed no significant difference between the 2 groups [7].

The results of a single study like this cannot serve as a general basis for making medical decisions. On one hand, therapeutic effects can be overlooked when the number of cases is relatively small (n=error), and on the other hand, strict selection of patients may exert a strong influence so that the results cannot be easily generalized. Decision finding can be facilitated by reproducible results and trend analyses of other studies. We, therefore, compiled data on therapeutic effects as reported in other studies on adjuvant treatment of gastric cancer. In doing this, the findings obtained in European and Anglo-American countries have to be distinguished from those of Japanese studies, especially since the results obtained with primary therapy of gastric carcinomas are, in general, more favorable in Japan than in European or Anglo-American countries [11, 12]. Beside possible differences in tumor biology and the stage of disease, differences in the primary treatment have to be taken into account.

The more favorable therapeutic results obtained in Japan seemed to be predominantly due to the very strict rules for surgical procedures that were set up by the Japanese Research Society for Gastric Cancer [13]. By obeying these rules, it was possible to achieve an improved primary therapy with refined operative strategies in Western countries [14, 15]. The advantage of standardized surgery also comprised a more accurate staging so that marginal therapeutic improvements can perhaps be better documented in clinical studies.

### The Positive Japanese Experience

Mitomycin C is one of the most effective drugs used in Japanese studies on adjuvant therapy of gastric cancer [16–18], but toxicity of this substance is critical [19]. Furthermore, Moertel [20] expressed general reservations against the efficacy of mitomycin C as an adjuvant treatment in gastric cancer: "Japanese investigators have conducted a great array of controlled studies involving many thousands of patients. Most of these studies have incorporated mitomycin-C and results have been inconsistent. Although a number of Japanese investigators maintain an enthusiasm for mitomycin-C, I would think the evidence indicates that any benefit from this agent has been, at best, highly equivocal."

Many of the Japanese treatment protocols utilized mitomycin C in combination with fluorinated pyrimidines [21, 22]. Several of these have also suggested a significant survival advantage for...