Chemotherapy in Gastric Cancer: A Brief Chronicle with Emphasis on Recent Developments

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The incidence of carcinoma of the stomach has declined in the western world over the last few decades. Nevertheless, about 21,000 new cases are still diagnosed yearly in the United States alone. Worldwide, carcinoma of the stomach remains one of the leading malignancies.

The developmental history of chemotherapy in advanced gastric cancer parallels that of anticancer chemotherapy as a whole. Single-agent activity was identified in the 1970s for a number of drugs, including 5-fluorouracil, mitomycin-C, adriamycin and the nitrosoureas, and later, cisplatin, etoposide (VP-16) and epirubicin. Response rates to single-agent chemotherapy were in the range of 15–20%, and remissions were mostly short lasting and had a marginal impact on patients' survival. Early efforts with combination chemotherapy trials date back to the late 1970s as well, culminating with the publication in 1980 of results obtained with the FAM regimen (5FU, adriamycin, mitomycin), which, following a 42% remission rate, became at the time the gold standard combination for the treatment of advanced gastric cancer, and in fact signaled it as a chemosensitive disease [1]. Further trials with the FAM combination were less successful, and indeed a study by Cullinan et al. [2] from the Mayo Clinic published in *JAMA* in 1985 showed that while combination chemotherapy (FAM, adriamycin-mitomycin) results in higher response rates than 5FU alone, the overall survival was similar for all three treatment arms. The setback resulting from the Cullinan trial prompted several studies in which combination chemotherapy proved to be superior when compared with supportive care alone in patients with advanced gastric cancer in terms of overall survival [3]. Other frequently used drug combinations in the 1980s included etoposide with 5FU and leucovorin with or without cisplatin; cisplatin and 5FU with leucovorin. The combination of etoposide, adriamycin and cisplatin represented the first non-5FU-containing regimen in routine use for the treatment of gastric cancer [4]. Experience was gained from a substantial number of phase II clinical trials where results were rather homogeneous, with response rates in the range of 35–45% and median survival times ranging from 7 to 9 months from the onset of chemotherapy.

Clinical investigations in Europe reported promising results with the combination of moderately high doses of methotrexate and 5FU with leucovorin and adriamycin, the so-called FAMTX regimen [5]. In a further developmental milestone in the treatment of advanced gastric cancer, several comparative clinical trials were carried out in the 1990s in an attempt to identify in randomized phase III studies the best available combination. FAMTX proved to be superior to both FAM [6] and EAP [7], but in a third trial was inferior to the combination of an anthracycline, epirubicin, given with cisplatin, and with 5FU, the latter as an uninterrupted, continuous intravenous infusion, the ECF regimen, which resulted in a response rate of 45% as compared to 21% with FAMTX [8]. While the issue of a standard combination regimen in advanced gastric cancer remains unsettled, the inclusion of cisplatin with long-term exposure to a fluoropyrimidine seems pivotal. Several novel cytotoxic drugs were introduced into the clinic in the latter part of the 1990s, some of which proved to be active in gastric cancer, including the taxanes, docetaxel (Taxotere®) and paclitaxel (Taxol®); irinotecan (CPT-11) and the oral fluoropyrimidines, uracil-ftorafur and capecitabine (Xeloda®).

Response rates to combination chemotherapy in metastatic gastric cancer reach 35–50%; median survival remains less than one year. Postoperative (adjuvant) radiochemotherapy programs appear to improve outcome in locally advanced primary gastric cancer.

I shall briefly review the process of incorporation of these newer agents into the armamentarium in use against gastric cancer, and their current status both in advanced disease and to a lesser degree in the adjuvant setting. Of 42 clinical trials in metastatic gastric cancer reviewed by Hasham-Jiwa et al. [9] carried out in North America and Europe between January 1995 and December 2001, 27 included at least one of the newer chemotherapeutic drugs; the vast majority, 22, are phase II trials and only 5 are phase III studies.

5FU = 5-fluorouracil
FAM = 5FU, adriamycin, mitomycin

EAP = etoposide, adriamycin, cisplatin
FAMTX = methotrexate, 5FU, leucovorin, adriamycin

Table 1. Single-agent activity of Taxotere® in advanced gastric cancer

	Author	Year	Ref.	No. of patients	Dose of Taxotere® (mg/m^2)*	Response rate
Previously untreated patients	Sulkes	1994	[10]	32	100	24%
	Einzig	1996	[35]	41	100	18%
	Mavroudis	2000	[36]		100	20%
	Bang	2002	[37]	44	75	18%
Previously treated patients	Taguchi	1998	[38]	45	60	20%
	Vanhoefer	1999	[39]	25	100	20%

* IV once every three weeks

Docetaxel (Taxotere®)

Docetaxel is a semisynthetic drug obtained from the needles of the European yew, *Taxus baccatta*. It acts by stabilizing the microtubular network in the malignant cell, thus disrupting essential cellular functions, including their ability to divide. Docetaxel is active in a number of malignancies including breast, lung, prostate, and head and neck cancers, among others; its dose-limiting toxicity is myelosuppression, typically neutropenia.

Early attempts at identifying the activity of docetaxel in gastric cancer were carried out in the mid 1990s. An initial phase II trial from the EORTC (European Organization for the Treatment and Research of Cancer) revealed a partial remission rate of 24% in previously treated patients [10], thus identifying docetaxel as a potentially active drug in this disease. Additional phase II trials of docetaxel as a single agent both in previously untreated patients and in those exposed to prior chemotherapy are summarized in Table 1. In general, the administration of one line of prior chemotherapy does not appear to be detrimental to the activity of docetaxel as a single agent in advanced gastric cancer, with response rates in the order of 20%. Several trials investigated the co-administration of docetaxel with other drugs active in gastric cancer, including cisplatin and 5FU. Trials in which docetaxel was given with cisplatin resulted in response rates ranging from 33 to 56% with median survival times of 9–10 months [11].

Results of a phase III randomized trial in 232 patients with advanced gastric cancer, comparing cisplatin and 5FU given as a continuous intravenous infusion with or without docetaxel, were recently presented at the Annual Meeting of the American Society of Clinical Oncology. Response rates and overall survival favored the inclusion of docetaxel; as expected, the three-drug regimen resulted in more pronounced leukopenia [12]. A phase III clinical trial sponsored by the European School of Oncology is ongoing where docetaxel in combination with either cisplatin alone or cisplatin with 5FU is being compared with a non- docetaxel-containing regimen, ECF.

Paclitaxel (Taxol®)

Paclitaxel is a natural product obtained originally from the Pacific yew, *Taxus brevifolia*. Its mechanism of action is similar to that described for docetaxel. Dose-limiting toxicities of paclitaxel are myelosuppression and, with prolonged use, peripheral neuropathy. Its range of activity includes a variety of malignancies such as breast, ovarian and lung cancer, head and neck tumors and germ cell malignancies. Single-agent activity of paclitaxel in metastatic gastric cancer has ranged between 5% and 23% [13].

A few trials have utilized paclitaxel in combination with cisplatin with/without the addition of 5FU and leucovorin. Response rates in these trials were remarkably similar and ranged between 44 and 48% with 11–14% of the patients achieving a complete remission, and a median survival of 11 months for all patients [14,15]. Peripheral neuropathy and neutropenia were dose-limiting.

Irinotecan (CPT-11)

Irinotecan, a camptothecin derivative, is a topoisomerase I inhibitor and as such causes irreparable DNA damage. Its main toxicities are hematologic and gastrointestinal, mainly diarrhea. Diarrhea may occur during administration of the drug or shortly thereafter due to a cholinergic type of reaction that responds promptly to the administration of atropine, or it can be delayed and develop later in the treatment cycle due to injury to the bowel's mucosa. CPT-11 represents a much needed and pivotal addition to the narrow list of drugs active against large bowel cancer. It has also shown activity in bronchogenic carcinoma and in esophageal and pancreatic tumors.

The activity of CPT-11 as a single agent in advanced gastric cancer was investigated in a phase II multicenter trial with the participation of Israeli institutions; 35 previously untreated patients with measurable disease received CPT-11, 350 mg/m^2 every 3 weeks. A 20% response rate was observed including two complete remissions; neutropenia and diarrhea were the most frequent side effects [16].

Most of the available information on the use of CPT-11 in combination chemotherapy regimens in gastric cancers derives from trials carried out at the MD Anderson Cancer Center in Houston by Ajani and collaborators [17,18]. Initially, CPT-11 was combined with cisplatin and given to 29 patients who had failed one line of prior chemotherapy [17]. In this unfavorable setting a 31% response rate was obtained, prompting the use of this regimen in previously untreated patients [18]; a total of 36 patients were treated with these two drugs and a 58% response rate was observed including an 11% complete remission rate. Side effects included mainly fatigue, diarrhea and myelosuppression. In a recent European trial, CPT-11 was combined with either cisplatin or 5FU-leucovorin, the latter resulting in a higher response rate (34% vs. 28%) and a more prolonged median survival (11 vs. 7 months, respectively). These investigators are now comparing CPT-11, 5FU and leucovorin against cisplatin and 5FU as the "standard" arm.

Hawkins and colleagues [19] compared CPT-11 and docetaxel with docetaxel and 5FU in a group of 65 patients with advanced gastric cancer. Response rates reached 38% in the CPT-11 arm and 33% for the docetaxel-5FU combination. Median survival was 9 months in both arms, but patients receiving CPT-11 had a higher incidence of diarrhea and neutropenic fever.

ECF = epirubicin, cisplatin, 5FU

Oral fluoropyrimidines

The clinical observation of an improved therapeutic index for 5FU when given as a protracted intravenous infusion prompted in recent years the enhanced development of the oral fluoropyrimidines, which in fact achieve a continuous exposure to the active compound, mimicking a prolonged infusion of 5FU but overcoming the logistic problems associated with long-term IV infusions such as the need for a patent venous access and the use of portable pumps.

UFT (uracil-ftorafur) was synthesized in Japan in 1978. Uracil is a potent inhibitor of dihydropyrimidine dehydrogenase, the main catabolic enzyme of 5FU; thus, an increased amount of 5FU is available for its cytotoxic activity. As a single agent, UFT is typically given daily for 4 consecutive weeks followed by a 1 week rest before the onset of a subsequent cycle. Its main potential toxicity is diarrhea. UFT is active in a variety of solid tumors such as colon and other gastrointestinal cancers and head and neck malignancies.

In 1998 Takiuchi and Ajani [20] reviewed the worldwide experience with UFT in advanced gastric cancer. Pooled data from Japanese phase II clinical trials included 188 patients in whom a 28% response rate was obtained; the median survival for all patients was about 6 months, reaching 9 months for those who achieved a response to UFT. With regard to the use of UFT in combination with other drugs, Japanese investigators reported a 25% response rate for UFT and mitomycin, a 43% rate with UFT and cisplatin, and a 50% remission rate with UFT, mitomycin, cisplatin and etoposide. An early phase II clinical trial was conducted in Spain in 46 patients with advanced gastric cancer who received UFT, leucovorin and etoposide; 35% experienced an objective remission for a median of 10 months [21].

More recently, Seymour et al. [22] at St. Bartholomew's Hospital in London substituted 5FU for UFT in the ECF regimen and conducted a phase I-II trial with escalating doses of UFT given continuously throughout the treatment course, once every 12 hours; oral leucovorin was given on days 1, 8 and 15 of the cycle. The maximal tolerated dose of UFT was 300 mg/m^2 per day. At higher doses diarrhea became dose-limiting. Thirty patients with advanced disease participated in this trial, of whom 15 suffered from a gastroesophageal primary and had evaluable disease; 9 of the 15 patients (60%) achieved a remission, complete in 2, for a median of 9 months.

Capecitabine is a carbamate fluoropyrimidine derivative with a unique mechanism of action as it requires a three-step enzymatic activation, the last one occurring in the tumor tissue itself due to substantially higher concentrations of thymidine phosphorylase in the tumor as opposed to healthy peritumoral tissues. Capecitabine is given daily in two doses for 14 consecutive days every 3 weeks. Side effects include myelosuppression and, characteristically, hand and foot syndrome with palmo-plantar erythema that can evolve to marked desquamation with pain and discomfort, reversible upon discontinuation of the drug. Capecitabine is widely used in patients with breast and colon cancer. Clinical trials in colon cancer have revealed a favorable therapeutic index when compared to traditional 5FU-leucovorin regimens.

UFT = uracil-ftorafur

Regarding metastatic gastric cancer, Kim et al. [23] recently reported a response rate of 55% and a median survival of 10 months with a combination of cisplatin and capecitabine at full dose, as described earlier. A Scottish dose-finding and pharmacokinetic phase I clinical trial utilized fixed doses of epirubicin and cisplatin, with escalating doses of capecitabine [24]. These investigators have now launched a phase III trial of the all-IV older regimen ECF versus that of EC and capecitabine, the newer oral fluoropyrimidine substituting for IV 5FU.

Oxaliplatin

Oxaliplatin is a third-generation platinum compound introduced into the clinic in recent years as it is active as second or third-line chemotherapy in advanced colorectal cancer, in conjunction with 5FU and leucovorin. Activity has been shown for other solid tumors as well, such as lung, pancreatic, and head and neck cancers.

Experience with oxaliplatin in advanced gastric cancer remains scarce. A recently published French phase II trial by Louvet et al. [25] included 53 previously untreated patients with advanced gastric cancer. Oxaliplatin was given with a continuous IV infusion of 5FU over 2 days with cycles repeated every 2 weeks. The response rate in this trial reached 45% with a median survival of 9 months; 38% of the patients experienced grade III/IV neutropenia and 21% developed grade III neuropathy, oxaliplatin-induced.

Kim et al. [26] utilized the same regimen described above (except for a lower dose of oxaliplatin) as second line in 23 patients with advanced gastric cancer who had failed prior chemotherapy with 5FU and cisplatin. Remarkably, they observed a 26% partial remission rate, with a median survival of 7 months. Phase III studies with oxaliplatin in gastric cancer are not available at present.

Adjuvant chemotherapy

Adjuvant chemotherapy is given to patients at high risk of relapse following the resection of the primary tumor, at a time when they are clinically free of disease. This treatment modality is now standard in a variety of disease entities such as breast and colon cancers and osteogenic sarcoma.

Multiple attempts over the last 25 years with adjuvant treatments following resection of primary tumors of the stomach were generally unsuccessful. Therapeutic approaches included either systemic chemotherapy alone or in conjunction with radiation therapy delivered to the tumor bed, but none became standard care.

One particular study with positive results was recently updated by Grau and co-authors from Spain [27]. They reported on 314 patients with resected gastric cancer accrued between 1977 and 1998; 151 of these patients received no adjuvant therapy and 163 were given four cycles, 6 weeks apart, of mitomycin C alone (109 patients) or in combination with an oral fluoropyrimidine, ftorafur (54 patients). At last analysis, 52% of the patients given adjuvant chemotherapy remain alive as compared to 30% of those who did not receive postoperative chemotherapy ($P = 0.0001$).

Several meta-analyses have been carried out in the last decade to determine the efficacy of adjuvant therapy in order to reduce the odds of death from gastric cancer following surgery [28–31]. Each

analysis is based on 12–20 individual trials, together comprising between 2,000 and 3,000 patients. The trials were carried out either exclusively in the western world or include also Asian (mainly Japanese) studies. All show similar results with a relative risk of about 0.8 favoring postoperative treatment over observation only after surgery, indicating that adjuvant chemotherapy may help a fraction of patients with localized gastric cancer. Results of these meta-analyses translate into an absolute gain in survival of about 4% and a relative reduction in the risk of death from gastric cancer of about 18% with the administration of adjuvant treatment.

About 2 years ago, the Intergroup in the U.S. reported results of their 0116 trial of an adjuvant chemoradiotherapy program delivered to patients with a good performance status and a daily intake of 1,500 calories, who had undergone complete resection of a primary gastric carcinoma that had penetrated through the gastric wall to the serosa and/or had metastasized to the regional (perigastric) lymph node-bearing areas, but with clean surgical margins. The treatment program included one cycle of 5FU and leucovorin followed by radiation therapy to the tumor bed to a total of 4,500 cGy after which two more cycles of 5FU and leucovorin were administered. A total of 556 patients were randomized to either observation only following surgery or to chemoradiotherapy. At a median follow up of 3.3 years the authors reported a significant disease-free survival and overall survival advantage for the subgroup of patients receiving adjuvant therapy (49% and 52% vs. 32% and 41% respectively), for a relative improvement of 44% in relapse-free survival and of 28% in survival [32].

Of note, chemoradiotherapy resulted in a substantial reduction in locoregional recurrence (19% vs. 29% in the control arm) but not in systemic relapse, probably indicating that surgery was not adequate in many of these patients and that chemoradiotherapy was in fact therapeutic for this subgroup, eliminating residual disease. Indeed, as much as 54% of the patient population underwent less than the standard D_1 resection where lymph nodes of all perigastric stations are removed. This Intergroup study experienced other setbacks as well: in about one-third of the patients a central review committee found that the radiation therapy fields were inadequate. Furthermore, the treatment plan resulted in substantial toxicity, grade IV in 32% and grade III in 41% of the patients. Moreover, 3 patients (1%) in the adjuvant treatment arm experienced a toxic death and only 54% of the patients were able to complete the treatment program as originally planned. Nonetheless, and as a result of this trial, adjuvant treatment has now become standard for patients undergoing resection of primary gastric carcinomas who fulfill the inclusion criteria described earlier.

A National Cancer Institute-sponsored trial of patients who have undergone a curative resection of gastric cancer is underway to compare the chemoradiation regimen as given in the Intergroup trial just described, with the ECF regimen (three cycles, one prior and two after radiation therapy) with continuous infusion 5FU, 200 mg/m^2/day delivered throughout the radiation therapy course [33].

Other studies in the adjuvant setting in gastric cancer are now ongoing elsewhere, particularly in Europe [34]. These include two Italian trials, one in which patients are offered four cycles of cisplatin, etoposide, leucovorin and 5FU following surgery, and a second one where patients are randomized into two possible treatment arms postoperatively: 5FU-leucovorin alone versus PELF, the so-called GISCAD trial where there is no control (observation only) arm. The "Magic" trial is underway in the United Kingdom, comparing surgery alone with three cycles of ECF before and three additional cycles after surgery. The EORTC is conducting a large multi-institutional, multinational trial comparing surgery with surgery and cisplatin, 5FU and leucovorin. Finally, the initial groundbreaking studies incorporating one of the new cytotoxic agents into the adjuvant setting have been activated, one by the SAAK cooperative group in Switzerland, which is using a combination of cisplatin, 5FU and docetaxel, and an Italian trial where one of the treatment arms calls for the delivery of three cycles of CPT-11, 5FU and leucovorin followed by three cycles of cisplatin and docetaxel. In order to fully establish the therapeutic value of adjuvant programs in gastric cancer, further large confirmatory phase III trials will be necessary.

Concluding remarks

5FU-based combinations over the last two decades, including multiple clinical trials, have resulted in only marginal gains for patients with advanced gastric cancer. Median survival remains less than one year. Nevertheless, objective responses are now routinely observed in 35–50% of the patients, and the proportion of patients surviving beyond one year with metastatic disease is increasing. Recent results with the use of postoperative multimodality (chemotherapy and radiotherapy) programs in the adjuvant setting are encouraging and many trials are presently underway.

The incorporation into the clinic of several novel cytotoxic agents in recent years – while still not representing a breakthrough in advanced gastric cancer – is still in an early stage of development. It is anticipated that further trials with these drugs and the advent of newer agents now in the pipeline will ultimately result in an improvement in survival for patients with metastatic gastric cancer, as avenues other than chemotherapy such as a variety of biological approaches continue to be explored as well, both in advanced disease and in the adjuvant setting. The impact of these efforts shall hopefully translate into major progress in the treatment of gastric cancer in the next few years.

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PELF = cisplatin, etoposide, leucovorin, 5FU

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