TREATMENT OF GASTRIC CANCER FOR SURVIVAL –
STRATEGIES IN THE USA AND JAPAN

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Abstract
Chemotherapy has been shown to benefit patients with gastric cancer. The most effective regimen remains controversial. A recent large randomized clinical trial has demonstrated an advantage with the addition of docetaxel to 5-fluorouracil and cisplatin. New agents are being incorporated into the treatment of gastric cancer to maximize efficacy with minimal additional toxicity. Future clinical trials will explore the use of new agents as well as genetic polymorphisms that may influence drug metabolism and efficacy.

Introduction
Adenocarcinoma of the stomach is the second most common malignancy worldwide with an estimated 558,400 new cases and 405,200 deaths in 2003 (Bonin, Schwarz et al., 2003). An estimated 21,900 new cases are diagnosed annually in the United States with approximately 13,500 annual deaths (Landis, Murray et al., 1999; Boring, Squires et al., 1991). In the United States 5-year survival remains poor at 22% while in Japan, with improved screening, the 5-year survival is 50%, a reflection of diagnosis at an earlier stage. Despite earlier diagnosis gastric cancer remains the number
one cause of death in Japan. In addition, even for those who are surgically resected, the local and distant recurrence rate is 80%.

A high percentage of gastric cancer patients will benefit from systemic chemotherapy. There has been a trend toward improvement in 5-year survival from 15% in 1976 to 22% in 1998. Chemotherapy has been shown to improve survival compared to best supportive care. Four separate studies compared best supportive care to various chemotherapy combinations (Murad Santiago et al., 1993; Glimelius, Hoffman et al., 1994; Pyrhonen, Kuitunen et al., 1995; Scheithauer, Kornek et al., 1995). Each of these studies was terminated early due to a survival advantage in the chemotherapy arm. Survival ranged from 3 to 5 months in the best supportive care arm and 9 to 12 months in the treatment arms.

Since the 1970's a variety of chemotherapeutic agents have been evaluated in gastric cancer initially as single agents, and then in various combinations in the 1980's. A cumulative analysis of results from studies with over 650 patients who received 5-fluorouracil, doxorubicin, and mitomycin-c (FAM) showed a response rate of 30% with a 2% complete remission rate. Median remission durations ranged from 5 to 10 months (Preusser, Achterrath et al., 1988). In 1991, the combination of 5-fluorouracil, leucovorin, doxorubicin, and methotrexate (FAMTX) was compared to FAM in a phase III trial with results showing an improved response rate of 41% compared to 9% (p value <.0001) and improved overall survival of 10.5 months compared to 7.3 months, respectively (p value = 0.0004) (Wils, Klein et al., 1991). These data established FAMTX as the new standard of care for treatment of metastatic gastric cancer. Multiple phase III trials followed comparing FAMTX with other combinations. In 1999, a phase III trial in 256 patients compared FAMTX to epirubicin, cisplatin, and fluorouracil (ECF). ECF showed a superior response rate (45% compared to 21%, p value=.0002) and overall survival (8.9 months compared to 5.7 months, p value=.0009) (Webb, Cunningham et al., 1997). The results of this trial did not replicate those previously reported for the FAMTX combination. However, they did establish ECF as the standard of care in much of Europe and Canada. Various other combinations have reported similar response rates and survival, however none of these combinations has been confirmed as superior (Vanhoefer, Rougier et al., 2000; Ross, Nicolson et al., 2002).
Summary of Treatment Results

Recent trials in gastric cancer have examined combinations of active agents at differing schedules. A balance of efficacy and tolerability in combination therapy has been difficult, with no regimen unanimously recognized as superior. The following is a summary of results from many of the gastric cancer trials presented at the American Society of Clinical Oncology (ASCO) meeting in 2003.

Interim results of V325

A large international randomized phase III trial (V325) comparing docetaxel, cisplatin, and 5-fluorouracil (DCF) to cisplatin and 5-fluorouracil (CF) for chemotherapy naïve patients with metastatic or locally recurrent, unresectable adenocarcinoma of the stomach or gastroesophageal junction has completed accrual and the interim results were presented at the ASCO meeting in June 2003 (Ajani, Van Cutsem et al., 2003). This study was conducted in two stages. The first stage was a phase II study to determine the best arm to move forward to phase III. A randomized phase II study with 155 patients assessed the response rate and safety of two experimental regimens DCF and docetaxel and cisplatin (DC). The overall response rate for DCF and DC were 43% and 26%, respectively, and the toxicity profile was acceptable for both regimens. This phase II study highlights the importance of the inclusion of 5-FU in combination therapy for gastric cancer.

The phase III portion of the study randomized 460 patients with metastatic or locally recurrent cancer of the stomach or gastroesophageal junction to treatment with either DCF (docetaxel 75 mg/m² and cisplatin 75 mg/m² both given on day 1, and infusional 5-FU 750 mg/m² given days 1-5 every three weeks) or CF (cisplatin 100 mg/m² on day 1 and infusional 5-FU 1000 mg/m² given days 1-5 every four weeks). The primary endpoint was time to progression. Secondary endpoints included overall survival, response rate, and safety. Patient characteristics were well balanced in both arms with approximately 70% being male, 55% having > 5% weight loss, 63% having a Karnofsky performance score (KPS) of 90-100%, and most patients (97-98%) having metastatic disease. In both arms the majority of tumors were located in the body and antrum of the stomach (72% in the DCF arm and 63% in the CF arm) as opposed to the gastro-
### TABLE I
Recent Phase II Gastric Trials

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response rate</th>
<th>TTP</th>
<th>Median Survival</th>
<th>Grade 3/4 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan 70 mg/m² + Cisplatin 80 mg/m²</td>
<td>42%</td>
<td>--</td>
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<td>Neutropenia 66.7%</td>
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<tr>
<td>Shira 1992</td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea 16.7%</td>
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<tr>
<td>Irinotecan 70 mg/m² + Cisplatin 80 mg/m²</td>
<td>48%</td>
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<td>9 months</td>
<td>Neutropenia 57%</td>
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<td>Boku 1999</td>
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<td></td>
<td>Diarrhea 20%</td>
</tr>
<tr>
<td>Irinotecan 65 mg/m² + Cisplatin 30 mg/m²</td>
<td>58%</td>
<td>6 months</td>
<td>9 months</td>
<td>Neutropenia 27%</td>
</tr>
<tr>
<td>Ajani 2002</td>
<td></td>
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<td></td>
<td>Diarrhea 22%</td>
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<tr>
<td>Irinotecan 65 mg/m² + Cisplatin 30 mg/m²</td>
<td>57%</td>
<td>4.2 months</td>
<td>14.6 months</td>
<td>Neutropenia 46%</td>
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<tr>
<td>Ish 1999</td>
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<td>Diarrhea 11%</td>
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<tr>
<td>Irinotecan 65 mg/m² + Cisplatin 30 mg/m²</td>
<td>36%</td>
<td>--</td>
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<td>Neutropenia 22%</td>
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<tr>
<td>Ish 2003 (Prelim)</td>
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<td>Diarrhea 18%</td>
</tr>
<tr>
<td>Irinotecan 200 mg/m² + Cisplatin 60 mg/m²</td>
<td>28%</td>
<td>4.5 months</td>
<td>6.9 months</td>
<td>Neutropenia 66%</td>
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<tr>
<td>ILF¹</td>
<td>34%</td>
<td>6.5 months</td>
<td>10.7 months</td>
<td>Diarrhea 19%</td>
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<td>ILF²</td>
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<td>17%</td>
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<td>Neutropenia 18%</td>
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<tr>
<td>LV5FU2²</td>
<td>13%</td>
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<td>6.8 months</td>
<td>Neutropenia 11%</td>
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<td>LV5FU2 + P³</td>
<td>27%</td>
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<td>9.5 months</td>
<td>Neutropenia 61%</td>
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<td>40%</td>
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<td>11.3 months</td>
<td>Neutropenia 40%</td>
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<td>Diarrhea 22%</td>
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<td>Docetaxel 60 mg/m² + Irinotecan 250 mg/m²</td>
<td>37.5%</td>
<td>3.8 months</td>
<td>9 months</td>
<td>Neutropenia 85.4%</td>
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<td>Diarrhea 42.9%</td>
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<td></td>
<td>Fatigue 23.8%</td>
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<td></td>
<td>Stomatitis 14.3%</td>
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<td></td>
<td>Fluid retention 2.4%</td>
</tr>
<tr>
<td>Docetaxel 85 mg/m² + 5FU 750mg/m²/day x 5</td>
<td>33.3%</td>
<td>4.4 months</td>
<td>9.4 months</td>
<td>Neutropenia 69.8%</td>
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<tr>
<td>Hawkins 2003</td>
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<td></td>
<td>Diarrhea 16.3%</td>
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<td>Fatigue 11.6%</td>
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<td></td>
<td>Stomatitis 23.3%</td>
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<td>Fluid retention 14%</td>
</tr>
</tbody>
</table>

¹ Time to progression, ² Irinotecan 80 mg/m² + leucovorin 500 mg/m² + 5FU 2 grams/m² continuous infusion weekly x 6 then 2 off, ³ etoposide 120 mg/m² + leucovorin 300 mg/m² + 5FU 300 mg/m² every 3 weeks, ⁴ leucovorin 200 mg/m² + 5FU bolus 400mg/m² + 5FU 600mg/m²/day over 44 hours, ⁵ LV5FU2 + cisplatin 50 mg/m², ⁶ LV5FU2 + irinotecan 180 mg/m²
Figure 1: Pathway of irinotecan metabolism. Irinotecan is inactivated to APC (aminopentane carboxylic acid) by the glucuronidation pathway and activated to SN-38 by carboxyl-esterase-2 (CE2). SN-38 is responsible for the activity and toxicity observed with irinotecan. The UGT1A1 pathway inactivates SN-38. [Reprinted with permission from F. Innocenti and M. Ratain. Oncology: 17 (5 Suppl. 5) 52-55, 2003].

Figure 2: Mutations in the UGT1A1 Gene. UGT1A1 polymorphisms *27 and *28 are associated with increased toxicity with irinotecan. [Reprinted with permission from F. Innocenti and M. Ratain. Oncology: 17 (5 Suppl. 5) 52-55, 2003].
esophageal junction (GE junction) and fundus (28% in the DCF arm and 37% in the CF arm). The tumor sites are indicative of the international patient pool involved in the study, as the percentage of tumors in these locations is generally reversed in the US.

The study has completed accrual and results were presented for the 123 patients for the planned interim analysis after 162 events occurred. The primary endpoint, time to progression (TTP) included patients with progressive disease or death and was 5.2 months in the DCF arm compared to 3.7 months in the CF arm (p=0.0008). The secondary endpoint overall survival (OS) in the DCF arm was 10.2 months compared to 8.5 months in the control arm (p=0.0064). The overall response rate was 38.7% for DCF compared to 23.2% for CF (p=0.012).

The limitation of the DCF regimen is hematologic toxicity. National Cancer Institute common toxicity criteria (NCI CTC) grade 3 or 4 neutropenia was experienced by 84% of patients receiving DCF as compared to 60% of those who received CF. Febrile neutropenia and neutropenic infection were seen in 16% and 14%, respectively of patients in the DCF arm as compared to 6% and 7% in the CF arm. Non-hematologic grade 3 or 4 toxicities experienced more frequently in the DCF arm compared to the CF arm included neurosensory (8% compared to 5%), infection (12% compared to 6%), and diarrhea (20% compared to 8%). Grade 3 or 4 toxicities more frequently seen in the CF arm included nausea (20% compared to 14%), vomiting (21% compared to 15%), and stomatitis (30% compared to 23%). Death related to treatment was equivalent in each arm at 6.3% as determined by an independent steering committee.

The V325 international study interim results are very valuable as there is a paucity of randomized trials with significant numbers of patients evaluating chemotherapy combinations in gastric cancer. This study demonstrates the activity of newer drugs, i.e. docetaxel, in gastric cancer and verifies the efficacy of combination chemotherapy for treatment. DCF resulted in an improvement in the time to progression, overall response rate, and most importantly survival for good performance status patients with metastatic gastric cancer. The survival seen with this combination still does not reach one year highlighting the need for further work in this area. The toxicity seen with this regimen may also make it prohibitive as 84% of DCF patients experienced neutropenia with a significant number of febrile neutropenic occurrences and neutropenic
infections. Future studies will focus on attempts to reduce toxicity while maintaining efficacy.

**Irinotecan**

Multiple phase II studies have demonstrated the activity of irinotecan in cancer of the esophagus and the stomach (Table I). Two studies evaluating its use as a single agent in a small number of patients (21 and 34) showed a response rate of ~15% (Lin, Hecht *et al.*, 2000; Enzinger and Ilson 2000). Further improvement in the response rate has been reported when irinotecan was combined with other agents such as 5-FU and leucovorin (response rate 22%) (Findalay, Ackland *et al.*, 2001).

Cisplatin and irinotecan are both active as single agents in gastric cancer with differing mechanisms of action. The combination has demonstrated synergy *in vitro* by reducing removal of DNA cross-links. Two phase II trials evaluated the combination of irinotecan and cisplatin. Thirty six patients with previously untreated advanced adenocarcinoma of the stomach or gastroesophageal junction received irinotecan at 65 mg/m² and cisplatin at 30 mg/m² weekly for four weeks followed by two weeks of rest (Ajani, Baker *et al.*, 2002). Complete responses were reported in 11% and partial responses in 47% for an overall response rate of 58%. Median time to disease progression was 24 weeks and median survival was 9 months. Ninety percent of doses were delivered on time, however, 66% of canceled or delayed weekly doses occurred in the third or fourth week of treatment. A second trial evaluated previously untreated patients with unresectable or metastatic esophageal adenocarcinoma (23 patients) or squamous cell carcinoma (12 patients, Ilson, Saltz *et al.*, 1999). Cisplatin and irinotecan were given at the same schedule and doses as the previously reported study. A major objective response was reported in 57% of patients with 6% achieving a complete response. The median duration of response was 4.2 months (range 1 to 8.8 months) and the median survival was 14.6 months. Weekly therapy resulted in one third of treatment cycles being delayed due to hematologic toxicity with 46% of patients reported to experience grade 3 or 4 neutropenia. In response to this toxicity, the combination of irinotecan and cisplatin was evaluated at the same doses with a different schedule, given on days 1 and 8, every 21 days (Ilson, Graham *et al.*, 2003). Thirty-nine patients had been accrued to the trial and response data and toxicity data were reported for the first
cohort of patients. No complete responses were reported. Partial responses were seen in 36% and stable disease in 18%. Grade 3 or 4 hematologic toxicities included anemia (3%), leukopenia (19%), neutropenia (22%), febrile neutropenia (13%), and thrombocytopenia (3%). The change in administration to day 1 and day 8 of a 21-day cycle has thus far resulted in reduced hematologic toxicity, which is anticipated to result in improved delivery. Ongoing trials will help to confirm these results.

The combination of cisplatin and irinotecan has also been assessed in Japan. (Shirao, Shimada et al., 1997) A phase I/II trial evaluated the use of higher doses at another schedule. Irinotecan was given at 70 mg/m² on days 1 and 15 and cisplatin at 80 mg/m² on day 1 of a 28-day cycle. Responses were seen in 10/24 patients (42%). Grade 3 toxicities included neutropenia (66.7%), and diarrhea (16.7%). A phase II trial of the same regimen was then conducted with 44 patients with metastatic gastric cancer who may have received one previous therapy (29 were previously untreated)(Boku, Ohtsu et al., 1999). Median survival was 272 days. The overall response rate was 48% with one complete remission. Grade 3 or 4 toxicities included neutropenia (57% grade 4), diarrhea (20%) and nausea (18%).

Other phase II trials have explored alternative combinations of irinotecan, cisplatin, and docetaxel. A combination of irinotecan 200 mg/m² and cisplatin 60 mg/m² every three weeks was compared to irinotecan 80 mg/m², leucovorin 500 mg/m² and continuous infusion 5-FU 2 grams/m² weekly (ILF) in 148 previously untreated patients with advanced gastric or gastroesophageal adenocarcinoma (Pozzo, Bugat et al., 2001). As compared to cisplatin and irinotecan, ILF demonstrated an improvement in response rate (34 % compared to 28%), time to progression (6.5 months as compared to 4.5 months), median survival (10.7 months as compared to 6.9 months), and one-year survival (44% as compared to 23%). The cisplatin containing combination resulted in more grade 3/4 neutropenia (66% compared to 26%), however less grade 3/4 diarrhea (19% compared to 27%).

ILF has also been compared to the combination of etoposide 120 mg/m², leucovorin 300 mg/m², and bolus 5-FU 500 mg/m² (ELF) (Moehler, Siebler et al., 2003). ILF was given weekly for six weeks then two weeks off. ELF was given days 1-3 and 22-24 every six weeks. The preliminary results of this study were presented at ASCO
2003, however accrual is ongoing. Results were reported for 58 evaluable patients. A complete response was reported in 3% with ILF and 0% with ELF, and a partial response was seen in 32% with ILF and 17% with ELF. Gastrointestinal related grade 3 or 4 toxicities were more frequent in the ILF arm compared to ELF, specifically diarrhea (11% compared to 0%), nausea (18% compared to 7%), and emesis (9% compared to 2%). ELF resulted in more frequent neutropenia (36% compared to 11%), thrombocytopenia (7% compared to 2%), alopecia (20% compared to 4%), and thrombosis (4% compared to 2%). One treatment related death occurred in each arm. Preliminary results suggest that ILF is safe and well tolerated for outpatient therapy and may be a more effective therapy than ELF for advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction.

Study FFCD 9803 is a randomized phase II trial evaluating LV5FU2 (leucovorin 200 mg/m² and 5FU bolus 400 mg/m² day one, and 5FU continuous infusion over 22 hours at 600 mg/m²/day on days one and two), LV5FU2-P (LV5FU2 + cisplatin 50 mg/m²), and LV5FU2-I (LV5FU2 + irinotecan 180 mg/m²) in patients with metastatic gastric adenocarcinoma (Bouche, Raoul et al., 2003). No complete responses were reported. Partial responses were reported in 40% for patients receiving LV5FU2-I, 27% for patients receiving LV5FU2-P, and 13% for patients receiving LV5FU2 alone. The median overall survival with LV5FU2-I was 11.3 months, LV5FU2-P was 9.5 months, and LV5FU2 was 6.8 months. Grade 3 or 4 toxicities occurred most frequently in the LV5FU2-P arm including myelosuppression, nausea, and vomiting. Diarrhea and stomatitis were more frequent in the LV5FU-I arm. Alopecia was experienced only in the LV5FU-I group. Treatment was stopped due to toxicity in 14% in the LV5FU2-P arm, 4% in the LV5FU2-I arm, and 0% in the LV5FU2 alone arm. This study demonstrates the insufficient efficacy of LV5FU2 alone. The LV5FU2-I regimen was better tolerated than LV5FU2-P and showed an improvement in response rate and median overall survival. LV5FU-I will be further evaluated in a phase III study.

A phase II trial of non-platinum containing regimens compared docetaxel 60 mg/m² and irinotecan 250 mg/m² given on day one every three weeks to docetaxel 85 mg/m² day one and a 5-FU 750 mg/m²/day continuous infusion given over days one to five every three weeks (Hawkins, Cunningham et al., 2003). No significant difference
was reported in the overall response rate (37.5% compared to 33.3%), median time to progression (3.8 months compared to 4.4 months), or median survival (9 months compared to 9.4 months). Grade 3/4 toxicities occurred more frequently in the docetaxel and irinotecan arm compared to the docetaxel and 5-FU arm with the exception of fluid retention and stomatitis (14.3% compared to 23.3%, and 2.4% compared to 14%, respectively). Patients randomized to docetaxel and irinotecan experienced more neutropenia (85.4% compared to 69.8%), febrile neutropenia (26.8% compared to 16.3%), neutropenic infections (14.6% compared to 4.7%), diarrhea (42.9% compared to 16.3%), vomiting (9.5% compared to 0%), and fatigue (23.8% compared to 11.6%).

New Agents

In addition to the work evaluating the efficacy and tolerability of chemotherapy combinations, the incorporation of innovative new agents has been advanced. Gastrin peptides G17 and Gly-G17 act as growth factors for GI cancer cell lines both in in vitro and in vivo models. G17DT is a monoclonal antibody directed to the gastrin peptides fused to diptheria toxin (Makishima, Larkin et al., 1995). A phase I/II study evaluated G17DT in combination with 5-fluorouracil and cisplatin in patients with locally recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction (Hecht, Ajani et al., 2003). The phase I portion determined the best schedule for G17DT administration in combination with 5-FU and cisplatin (500ug intramuscular injection day 8 of cycles 1, 2, 3 and 7). Toxicity of G17DT consisted predominantly of mild to moderate reactions at the injection sites including three abscesses. The other toxicities were similar to that observed by patients receiving chemotherapy alone. Patient sera were tested for anti-G17 activity. An anti-G17 titer of ≥ 1U was achieved by 76% of the patients and was associated with an improvement in survival of 9.9 months compared to 2.3 months for non-responders. After adjustment for performance status the correlation between the anti-G17 response and survival remained statistically significant (p<0.001).

Bryostatin-1 is a macrocyclic lactone isolated from the marine animal Bugula neritina. This compound exerts multiple anti-neoplastic effects including activating protein kinase C, increasing cytokine production, stimulating bone marrow progenitor cells, and potentiating apoptosis. Preliminary results are available for a phase II study of
the combination of paclitaxel at 80 mg/m² on days 1, 8, and 15 with bryostatin-1 at 40 ug/kg on days 2, 9, and 16 in patients with metastatic or unresectable locally advanced adenocarcinoma of the stomach or gastroesophageal junction (Chang, Bleyer et al., 2003). Thirty-four patients were evaluated for response. Grade 3 or 4 myalgias and arthralgias unresponsive to treatment with gabapentin and prednisone resulted in the withdrawal of 5/34 patients. Other toxicities included mild myelosuppression, fatigue, rashes, and gastrointestinal toxicity. The combination of paclitaxel and bryostatin-1 resulted in a 29.5% overall response rate. Most of these responses were short lived with a median time to progression of 1.7 months.

Maintenance therapy has been explored with the use of marimastat. The matrix metalloproteinases (MMPs) 1, 2, 7, and 14 are over expressed in human gastric tissue. Expression of MMPs has been correlated with poor prognosis. Marimastat is an inhibitor of MMPs and has been shown to inhibit invasive tumor growth in human gastric cancer xenograft models. Patients with advanced gastric adenocarcinoma were randomized to receive either placebo or marimastat 10 mg twice daily for up to 18 months (Stuart, Hawkins et al., 2000). Prior chemotherapy was allowed if the patient had responded or had stable disease. The primary endpoint was overall survival, which was reported as 167 days for patients who received marimastat compared to 135 days for those who received the placebo (p=0.070). In addition, patients who received marimastat had an improvement in one-year survival (20% compared to 14% for the placebo group) and progression-free survival (102 days compared to 84 days, p=0.009). Patients who had received first-line chemotherapy prior to treatment with marimastat had better overall survival on marimastat (p=.045).

Pharmacogenomics

The possibility of increased susceptibility of Japanese patients to the toxicity of various chemotherapy agents warrants further investigation. Irinotecan and 5-fluorouracil are two agents in which the possible racial differences in metabolism have been investigated. The major toxicities of irinotecan are myelosuppression and diarrhea. The diarrhea is felt to be secondary to biliary excretion of SN-38, the active metabolite of irinotecan. A study in the United States failed to demonstrate a significant effect of
gender or race (Caucasian compared to African American) on risk for irinotecan toxicity (Gupta, Mick et al., 1997). Toxicity was correlated with reduced glucuronidation of SN-38. Uridine diphosphate glucuronosyltransferase isoform 1A1 (UGT1A1) is responsible for the glucuronidation of SN-38 (figure 1)(Iyer, King et al., 1998). It has been suggested that patients with low UGT1A1 activity are at an increased risk for toxicity from irinotecan. Asian populations may be at an increased risk of irinotecan toxicity due to polymorphisms of the coding region of UGT1A1 that are commonly found in Asian populations and which predispose to neonatal jaundice (figure 2)(Akaba, Kimura et al., 1998). A case-control retrospective review of 118 Japanese patients who received irinotecan investigated the association of UGT1A1 polymorphisms and irinotecan toxicity including grade 4 leukopenia and grade 3 or 4 diarrhea. Multivariate analysis suggest that being either homozygous or heterozygous for polymorphism UGT1A1*28 may be a significant risk factor for irinotecan toxicity (p<0.001)(Ando, Saka et al., 2000). In addition, all patients heterozygous for the UGT1A1*27 polymorphism experienced severe toxicity to irinotecan. Polymorphisms including UGT1A1*6, UGT1A1*29, and UGT1A1*7 did not appear to be associated with toxicity.

Racial differences have also been evaluated in the genes that control the expression of thymidylate synthase (TS), the enzyme targeted by 5-fluorouracil. Triple repeats in the tandem sequences of the promoter enhancer for TS result in increased TS expression in vitro. Marsh, et. al evaluated differences in TS enhancer region tandem repeats in Caucasian, southwest Asian, and Chinese healthy volunteers by PCR analysis (Marsh, Collie-Duguid et al., 1999). Homozygous triple repeat TS promoter enhancer regions were found in 67% of Chinese subjects, 40% of southwest Asian subjects, and 38% of Caucasian subjects. Both of the above studies suggest a potentially important genetic variation in the metabolism of the chemotherapy agents commonly used in the treatment of metastatic gastric cancer. None of the genetic polymorphisms and associated toxicity have been evaluated in prospective trials. Indeed, the addition of pharmacogenomic analysis of patients in future studies will assist in clarifying the association with toxicity and potentially evaluating efficacious and better tolerated doses for patients with these polymorphisms.
Conclusions

The future of gastric cancer therapy will need to encompass improved efficacy and tolerability, specific targeted agents, and further evaluation of pharmacogenomics to ascertain any genetic variations that confer enhanced efficacy or toxicity. The V325 study has shown an improvement in overall survival, however it still remains dismal at less than one year. Combinations found effective in the metastatic setting can then be evaluated in the adjuvant setting to potentially further impact upon survival. Indeed gastric cancer treatment requires further investigation and all patients should continue to be encouraged to participate in clinical trials.

References


