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Docetaxel delivers new management opportunities for gastrointestinal carcinomas

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The results of four phase II studies of docetaxel in cancers of the gastrointestinal tract are summarized. No prior chemotherapy was permitted except for adjuvant chemotherapy completed at least 1 year before entering the present study. In all studies, docetaxel was administered at a dose of 100 mg/m^2 given by intravenous infusion over 1 h once every 3 weeks, adjusted according to toxicity. Routine premedication for hypersensitivity reactions was given to most patients in the US study in colorectal cancer but not to patients in the three European studies in gastric, pancreatic and colorectal cancers. In a European Organization for Research on Treatment of Cancer – Early Clinical Trials Group (EORTC–ECTG) study in gastric cancer, 8 (24%) of 33 evaluable patients achieved partial remissions lasting for a median of 7.5 months. Responses occurred in a variety of metastatic sites. Forty-two patients were evaluable in a French study of docetaxel in pancreatic cancer. Partial responses were achieved in 6 (20%) of 30 patients with metastatic disease and 3 of 12 patients with loco-regional disease showed some improvement. Two studies in colorectal cancer—one European and one US—found that docetaxel had little or no activity in these patients. Three (9%) of 33 evaluable patients in the European study achieved responses (one complete and two partial) and none of 19 patients in the US study. Hematological toxicity was the dose-limiting adverse effect. Acute hypersensitivity reactions and fluid retention also occurred in some patients. In conclusion, docetaxel appears to be as effective as standard single-agent therapies for gastric and pancreatic cancers but to have minimal effect in colorectal carcinoma. Toxicities were generally manageable; premedication with corticosteroids may reduce the incidence and severity of acute hypersensitivity reactions and delay the onset of fluid retention.

Introduction

Gastrointestinal (GI) cancers represent nearly one-third of all tumors occurring and are a leading cause of cancer-related deaths.[1,2] Surgery represents the mainstay of treatment for early disease [3] but the outlook following resection is frequently poor as a result of metastatic progression.[4,5] Until recently, chemotherapy for the management of patients with these cancers was relatively ineffective. Most experience has been gained with 5-fluorouracil (5-FU), introduced more than 30 years ago, which achieves response rates of around 20% in patients with metastatic carcinomas of the colon, rectum and stomach.[6,7] Nevertheless, there are few complete responses to 5-FU and the impact on survival is minimal.[6,7] The majority of combination regimens containing 5-FU have done little to improve response rates compared to single-agent therapy.[8] One exception is the combination of leucovorin and 5-FU, which has been shown to increase response rates in patients with metastatic colorectal carcinoma but still has had little influence on survival.[9] Cisplatin has also shown some limited activity in gastric and pancreatic cancers but not in colon cancer,[10,11] while anthracyclines and methotrexate have some small degree of efficacy in gastric cancers alone.[12] There is thus a clear need for new, effective drugs in the management of GI cancers. Docetaxel is one such agent that has shown promise in phase II trials in a number of different tumor types, including cancers of the GI tract.

Phase II clinical trials in GI cancers

Six phase II studies have been carried out in Europe and the USA to investigate the safety and efficacy of docetaxel in advanced cancer of the pancreas (two studies), stomach (one study) and colon (three studies) (Table 1). Results of four of these studies—the gastric cancer trial, one of the studies in pancreatic cancer and two of the colorectal cancer studies—are discussed in some detail below.[4,13–16] (Final results are not yet available for the M.D. Anderson Cancer Center study

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in pancreatic cancer nor the Memorial Sloan-Kettering Cancer Center study in colorectal carcinoma.)

Patients and methods

In order to be included in these studies, patients had to have histologically proven gastric, colorectal or pancreatic carcinomas with at least one bidimensionally measurable target lesion, a performance status of ≤ 2 (WHO scale) or equivalent, adequate blood counts, and normal renal and hepatic function. No prior chemotherapy was permitted, with the exception of adjuvant chemotherapy completed at least 1 year before the present study. Informed consent had to be obtained from all patients.

Docetaxel was given according to the same schedule in all studies. Thus all patients received docetaxel at the recommended dose of 100 mg/m^2 in 250 ml of 5% dextrose or normal saline solution, administered by i.v. infusion over 1 h once every 3 weeks. The dose was adjusted according to hematological and other toxicities. Most patients enrolled in the US study were also given premedication with diphenhydramine (with or without dexamethasone) for acute hypersensitivity reactions, while those in the European trials received no such premedication. There was no routine prophylactic administration of antiemetics or growth factors in any of the studies.

All tumor measurements were carried out and responses classified according to WHO criteria and all final efficacy results were reviewed by an external panel of experts, including radiologists.

Results

Gastric cancer

Patients. Forty-two patients were registered for the EORTC–ECTG study of docetaxel in gastric cancer.[4] Of these, 37 were considered eligible (27 males and 10 females) and 33 were evaluable for efficacy. Patient characteristics are shown in Table 2. Eighteen of the 37 patients (49%) had not undergone surgery for removal of the primary tumor. In the remaining 19 patients, the interval between surgery and treatment with docetaxel ranged from 3 weeks to 30 months (median 8 months). None of the patients in this study had received any prior chemotherapy.

Response. Of the 33 evaluable patients, eight (24%) achieved a partial remission which lasted for a median of 7.5 months (Table 3). Duration of overall survival ranged from 3 to 17 months. Responses occurred in a variety of metastatic sites, with 55–90% reductions in size of measurable retroperitoneal lymph nodes (three patients), a 96% decrease in the size of skin nodules (one patient), a 94% reduction in mediastinal, presternal and supraclavicular masses (one patient), an 84% decrease in primary tumor size (one patient), and a reduction to non-measurable disease for liver and abdominal wall masses (one patient each, both of whom were still surviving at 11+ and 7+ months, respectively, when the study report was published). Six of the eight patients responded after only two cycles of docetaxel treatment.

There was no correlation between response to docetaxel and initial performance status, age, metastatic site, or degree of myelosuppression. However,

Table 1. Clinical trials of docetaxel in cancers of the GI tract

Site	Principal investigator	Institution / group; location
Gastric	A Sulkes [4]	EORTC–ECTG; Europe
Pancreatic	P Rougier [13,14]	Institut Gustave-Roussy; Villejuif, France
	R Pazdur	M.D. Anderson Cancer Center / Memorial Sloan-Kettering Cancer Center; Houston, Texas / New York
Colorectal	C Sternberg [15]	EORTC–ECTG; Europe
	N Kemeny	Memorial Sloan-Kettering Cancer Center; New York
	R Pazdur [16]	M.D. Anderson Cancer Center; Houston, Texas

EORTC–ECTG, European Organization for Research on Treatment of Cancer – Early Clinical Trials Group.

Table 2. Characteristics of patients entered into a phase II study of docetaxel in gastric cancer

No. of registered patients	42
No. of eligible patients	37
Median age, years (range)	59 (37–72)
Male / female	27 / 10
WHO performance status, median (range)	1 (0–2)
Sites of disease, no. of patients (%)	
Retroperitoneal nodes	16 (43%)
Primary tumor	13 (35%)
Liver	12 (32%)
Intra-abdominal / pelvic mass	3 (8%)

Reproduced with permission from Sulkes A, Smyth J, Sessa C, *et al.* Docetaxel (Taxotere®) in advanced gastric cancer: results of a phase II clinical trial. *Br J Cancer* 1994; **70**: 380–383.

Table 3. Response to docetaxel in evaluable patients with gastric, pancreatic or colorectal cancers [4,13–16]

Response	No. (%)	Duration of response (months)	
		Median	Range
Gastric cancer (n = 33) [4]			
PR	8 (24)	7.5	3–11+
SD	11 (33)	4	3–8
PD	14 (42)	—	—
Pancreatic cancer [13,14]			
Metastatic (n = 30)			
PR	6 (20)	7	
SD	8 (30)	NA	
PD	13 (48)	—	
Locoregional (n = 12)			
Improvements [a]	3 (25)	11	
SD	3 (25)	NA	
PD	6 (50)	—	
Colorectal cancer			
EORTC–ECTG study (n = 33) [15]			
CR	1 (3)	54 weeks	
PR	2 (6)	NA	
CR+PR	3 (9)	NA	
SD	9 (27)	NA	
PD	21 (64)	—	
MD Anderson study (n = 19) [16]			
Minor response	2 (10.5)	—	

NA: not available. [a] Improvements not measurable physically but indicated by improved performance status and reductions in CA 19–9 levels.

Table 4. Patient characteristics in a study of docetaxel in pancreatic cancer [13,14]

No. of eligible patients	42 (of 43 registered)
No. of patients evaluable for efficacy	42
No. of patients evaluable for safety	24
Age (years), median (range)	59 (36–76)
Male / female	26 / 17
WHO performance status, median (range)	1 (0–2)
Disease extent	
Loco-regional only	12
Metastatic	30

responses seemed to occur more frequently in patients who had undergone surgical resection of the primary tumor than in those who had not (7/19 [37%] vs 1/18 [5%], respectively; $p = 0.06$).

Adverse events. The dose of docetaxel had to be reduced in 30 (19%) of the 156 cycles given, largely as a result of myelosuppression or skin toxicity. Grade 3–4 neutropenia occurred in 35 patients (95%), although leukopenic fever requiring hospitalization occurred in only eight cycles (5%). This reflected the prompt recovery of leukocyte counts (within 1 week of the nadir). Twenty-one patients experienced mild to moderate skin toxicity, consisting mainly of desquamation, dryness, pruritus and maculopapular rash. Acute hypersensitivity reactions in the form of flushing, rashes and, sometimes, shortness of breath occurred in nine patients, mostly shortly after initiation of the first docetaxel infusion; these effects were all mild or moderate in severity and none led to discontinuation of docetaxel. Fluid retention resulted in weight gain of > 2 kg in eight patients, with development of peripheral edema and some pleural effusions. All eight patients had received at least four cycles of docetaxel. Alopecia was the most frequently observed non-hematological side effect but was only grade 1–2 in severity. Other grade 3 toxicities consisted of fatigue and asthenia (16% of cycles), stomatitis (5%), nausea (3%), vomiting (3%) and cardiac dysrhythmias (3% grade 3 and 3% grade 4).

Discussion. The authors of this trial in patients with advanced gastric cancer concluded that docetaxel is an active agent in this setting, achieving a response rate similar to that seen with the most active conventional drugs when used as single agents (5-FU, doxorubicin, cisplatin and mitomycin C). The lower response rate in patients whose primary tumor had not been removed surgically probably reflected more advanced disease with a greater tumor burden compared to patients who had undergone surgical resection. Further trials of docetaxel in gastric cancer were considered to be warranted, including combination regimens with other active drugs in this setting. Routine premedication may help to prevent the hypersensitivity reactions and fluid retention and concomitant administration of granulocyte colony-stimulating factors may help to alleviate the myelosuppression.

Pancreatic cancer

Patients. Forty-three patients have been entered into the French study of docetaxel in carcinoma of the pancreas, of whom 42 were evaluable for efficacy (Table 4).[13,14]

Response. Six of the 30 evaluable patients with metastatic disease (20%) achieved a partial remission (Table 3). Median survival ranged from 212 days in patients with metastatic disease to 442 days in those with locally advanced pancreatic cancer only. Among the 12 patients with loco-regional disease, three showed improvements (a nonmeasurable decrease in tumor size indicated by a reduction in CA 19–9 levels and improved performance status), three had stable disease and six progressed.

Adverse events. Preliminary safety data are available for 24 patients and 99 cycles.[13,14] Adverse events experienced at the grade 3–4 level included neutropenia (83% of cycles), anemia (9%), infection (2%) and vomiting (1%). Grade 1–2 acute hypersensitivity reactions occurred in 6% of cycles and moderate to severe asthenia in 41.5% of cycles. Fluid retention was mild to moderate in 25% of patients and severe in 12.5%, with a median delay to onset of five cycles; three patients discontinued docetaxel because of edema.

Discussion. The results of this study suggest that docetaxel is a promising new agent for the treatment of pancreatic adenocarcinomas. Further studies should be undertaken to compare the activity of docetaxel with that of 5-FU and/or cisplatin. Routine premedication with corticosteroids may also improve the safety profile.

Colorectal cancer

Patients. In the two completed studies of docetaxel in colorectal carcinoma, a total of 58 patients were considered eligible (39 in the EORTC–ECTG study[15] and 19 in the M.D. Anderson Cancer Center study[16]). Patient characteristics for the two studies are shown in Table 5.

Table 5. Patient characteristics in two studies of docetaxel in colorectal carcinoma[15,16]

	EORTC–ECTG study[15]	M.D. Anderson Cancer Center study[16]	Total
No. eligible patients	39	19	58
No. evaluable patients	33	19	52
Male / female	23 / 16	11 / 8	34 / 24
Age (years), median (range)	60 (41–75)	54 (35–75)	57 (35–75)
WHO performance status, median (range)	1 (0–2)	1 (0–2)	1 (0–2)
Prior adjuvant chemotherapy	4	2	6
Sites of measurable disease			
Liver	26	18	44
Lymph nodes and abdominal / peritoneal masses	13	6	19
Lung / mediastinal masses	10	5	15
Subcutaneous nodes	4	—	4

Response. Among the 52 evaluable patients there were only three responses of any note (one complete and two partial), all of which occurred in the EORTC–ECTG study (Table 3).[15,16] Median time to progression among the 33 evaluable patients in the EORTC–ECTG study was 1.5 months, with a median survival duration of 7.5 months.[15] In the M.D. Anderson Cancer Center study there were just two minor responses, lasting for 14 and 6 weeks, respectively.[16] Median survival duration for all 19 patients was 12 months.[12]

Adverse events. Hematologic and skin toxicity were the main dose-limiting effects in these studies. Among the 58 patients evaluable for toxicity, 171 cycles of docetaxel were given.[11,12] Dose reduction, mainly to 75 mg/m^2, was necessary in 29 of the 118 cycles in the EORTC–ECTG study and in two of the 43 cycles in the M.D. Anderson Cancer Center study. Grade 3–4 leukopenia and neutropenia occurred in 41% and 85% of the EORTC–ECTG study patients, respectively, while grade 3–4 granulocytopenia was observed in 89% of the US study patients. Skin reactions (all grade 1 or 2) occurred in 39 of the 58 patients. Alopecia was almost universal although no patient experienced worse than a grade 2 effect. Mild to moderate fatigue was also experienced quite commonly (around two-thirds of patients) and roughly half the patients had GI upsets of some form (including nausea, vomiting, diarrhea and stomatitis), which were mostly grade 1 or 2. Fluid retention in the form of peripheral edema or pleural effusion was reported in six patients and one patient, respectively. Grade 3–4 hypersensitivity reactions occurred in 17 (33%) patients (five in the EORTC–ECTG study and 12 in the US study), mainly during administration of the first cycle of docetaxel. In seven of the 12 US study patients, these reactions occurred despite premedication with diphenhydramine. In contrast, acute hypersensitivity reactions were relatively uncommon in the EORTC–ECTG study even though no routine premedication was given.

Discussion. Although one patient in the EORTC–ECTG study achieved a complete response to doce-

taxel, this agent generally appears to have minimal activity against colorectal carcinoma. Only a few patients experienced an objective response in the two available phase II trials (0% and 9%, respectively). However, these response rates are not much lower than those reported in the recent well conducted randomized trial of 5-FU (range 8–12%) and in a recently reported meta-analysis.[9] Toxicities were similar to those reported elsewhere for docetaxel, with a relatively low frequency of acute hypersensitivity reactions, even in patients not receiving prophylactic premedication.

Conclusions

Docetaxel appears to be a promising new drug for the treatment of patients with advanced pancreatic and gastric cancers, achieving similar response rates to those seen with the most active conventional agents in these diseases. In contrast, docetaxel appears to have little activity in colorectal carcinoma but it should be tested in combination with 5-FU before being abandoned for this indication. Toxicities were generally manageable; premedication with corticosteroids may reduce the incidence and severity of acute hypersensitivity reactions and delay the onset of fluid retention. Administration of colony-stimulating factors may also reduce the incidence and severity of myelosuppression.

Studies should now be undertaken to compare the efficacy of docetaxel with that of the other active agents in these cancers and also to evaluate the benefits of combination therapy. Docetaxel should therefore be compared to and combined with 5-FU or cisplatin in pancreatic cancer, and with 5-FU, platinum, high-dose methotrexate and/or anthracyclines in gastric cancer.

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