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ORIGINAL ARTICLE

A phase II study of pegylated-camptothecin (pegamotecan) in the treatment of locally advanced and metastatic gastric and gastro-oesophageal junction adenocarcinoma

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Abstract
Purpose Combination chemotherapy results in a significant survival advantage in patients with advanced gastric cancer compared to best supportive care. Nevertheless, the prognosis remains poor with a median survival of 8–10 months. Topoisomerase-I inhibitors such as irinotecan have activity in advanced gastric cancer. Pegamotecan may offer significant advantages over other topoisomerase-I inhibitors due to its prolonged circulating half-life, tolerability and passive tumour accumulation.
Patients and methods This was a non-randomised, multicentre, two-step Fleming design phase II study. Eligible patients with locally advanced (inoperable) or metastatic gastric or gastro-oesophageal adenocarcinoma, with measurable disease, ECOG performance status ≤ 2, with adequate haematological, renal and hepatic function, who had received ≤ 1 prior chemotherapy regimen for advanced disease, were treated with 7,000 mg/m^2 of pegamotecan as a 1-h infusion every 21 days until disease progression or unacceptable toxicity. The primary efficacy measure was the objective response rate.
Results Five of the 35 patients recruited into this study had a partial response (14.3%), with a median time to progression of 11.9 weeks (95% CI: 6.6, 13.1), and median overall survival of 38.1 weeks (95% CI: 29.0, 47.3). Grade 3/4 toxicities included neutropenia in 6 (17.1%) patients, thrombocytopenia in 4 (11.4%), fatigue in 8 (22.9%), nausea in 6 (17%), vomiting in 6 (17%) and anorexia in 4 (11.4%) patients. There were no episodes of febrile neutropenia and no toxic deaths.
Conclusions Pegamotecan has activity in this patient population and was generally well-tolerated. The favourable rate of haematological toxicities and diarrhoea compared with irinotecan in similar studies suggests that pegamotecan could be combined with other active agents in further studies in this disease.

Keywords Pegamotecan · Gastric adenocarcinoma · Phase II · Clinical trial

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Introduction

Gastric cancer is the second leading cause of cancer mortality in the world, accounting for approximately 24,000 and 10,400 newly diagnosed cancers each year in the United States of America (USA) and the United Kingdom (UK), respectively [1]. Although there has been a decline in incidence of gastric cancer in Western countries over the past few decades, this has been accompanied by an increase in the incidence of tumours of the gastro-oesophageal junction and a shift towards poorly differentiated adenocarcinomas [2].

The vast majority (80–90%) of patients present with locally advanced or metastatic disease that is unsuitable for curative resection. Combination chemotherapy results in a significant survival advantage in patients with advanced gastric cancer when compared with best supportive care in randomised clinical trials [3–5]. High response rates may be obtained in these tumours by the use of protracted venous infusional 5FU, epirubicin and cisplatin—the ECF regimen [6]. In a multi-centre randomised study, ECF resulted in a significantly better response rate (45%) and median survival, with significantly less toxicity, compared to the FAMtx regimen [7]. However, this regimen may not be suitable for patients with co-morbidities such as renal or cardiac disease [8]. More recently, the addition of docetaxel to cisplatin and 5-fluorouracil (DCF) significantly improved response rates, time to disease progression and overall survival compared to cisplatin and 5-fluorouracil, although with some increase in toxicity [9]. Nevertheless, median survival remains poor in these patients treated with either the ECF regimen (8.9 months) [7] or with DCF (9.2 months) [9]. Consequently, novel agents with activity in gastric adenocarcinoma are required.

Topoisomerase-I inhibitors, such as camptothecin, irinotecin and topotecan exert their anti-proliferative activity during S-phase of the cell cycle where drug induced cleavable complexes result in the formation of double-stranded DNA breaks. Irinotecan monotherapy has response rates of between 14 and 23% in patients with advanced gastric cancer [10, 11]. In contrast, topotecan has only minimal activity in patients with advanced gastric cancer in phase II studies [12, 13]. Pegylated camptothecin (pegamotecan, Enzon, Piscataway, NJ) is synthesised by conjugating polyethylene glycol macromolecules to the 20-hydroxyl group of camptothecin. This produces a highly water-soluble and stable pro-drug which is activated by hydrolysis releasing camptothecin into tissues and biological fluids [14, 15]. Pegamotecan, however, may offer significant advantages over currently approved topoisomerase I inhibitors owing to its prolonged circulating half-life, tolerability, and passive tumour accumulation due to its high molecular weight [16, 17]. In pre-clinical studies pegamotecan demonstrated broad activity against human tumour xenografts of colon, lung, breast and pancreatic origin, and its efficacy was superior to that of topotecan and irinotecan in several of these tumour models [16].

Pegamotecan was administered as a 1 h intravenous infusion every 3 weeks at doses ranging from 600 to 8,750 mg/m^2 in a phase I clinical trial [18]. Dose limiting toxicity included NCIC-CTC grade 4 neutropenia and severe thrombocytopenia in two out of three patients treated with 8,750 mg/m^2. Consequently a dose of 7,000 mg/m^2 was recommended for subsequent phase II studies. There was a paucity of non-haematological toxicities with repeated administration at this dose level and with the slow clearance of camptothecin enabling simulation of desirable pharmacokinetic parameters with a convenient single-dosing regimen, we performed a phase II study to evaluate the objective response rate of pegamotecan administration in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinomas.

Patients and methods

Study design

This was a non-randomised, multi-centre, two-step Fleming design [19], phase II study of pegamotecan in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. The primary objective was to evaluate the objective tumour response rate of pegamotecan in this patient population, and secondary objectives included time to response, duration of response, time to disease progression, 3, 6, and 12 month and overall survival, safety and tolerability profile, and clinical benefit as measured by improvement in performance status, increase in weight, and symptom assessment.

Eligibility criteria

Eligible patients were those with histologically or cytologically confirmed, locally advanced (inoperable) or metastatic gastric or gastro-oesophageal junction adenocarcinomas. All patients had measurable disease, as defined by the response evaluation criteria in solid tumours criteria (RECIST) [20], ECOG performance status $\leq$2, were at least 18 years of age, and had adequate renal (serum creatinine concentration $\leq$1.5 mg/dl), hepatic [serum total bilirubin $\leq$1.5 or <3.0 mg/dl if due to metastatic disease in the liver, with serum AST/ALT $\leq$ 2.5 $\times$ upper limit of normal (ULN) or $\leq$5.0 $\times$ UNL in case of liver metastases], and haematological [absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l and haemoglobin $\geq$10.0 g/dl] function. Patients were excluded if the

serum albumin was ≤2.8 g/dl and if there was a history of haemorrhagic cystitis or evidence of microscopic haematuria (≥10 RBCs/high power field) on urinalysis. Prior systemic treatment, including investigational drugs, surgery or radiation therapy were allowed provided that these treatments had been completed at least 4 weeks before entry into the study. Other exclusion criteria included prior treatment with more than one chemotherapy regimen for locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma, prior treatment with a camptothecin analogue (e.g. topotecan, irinotecan), known clinical evidence of CNS metastases, patients who were pregnant or of child-bearing potential and unwilling to use an acceptable method of birth control, patients who were lactating, clinical evidence of serious inter-current disease, active or uncontrolled infection, or major organ failure.

This study was approved by the Research Ethics Committees of all participating institutions, and all patients gave written, informed, consent prior to any study related procedure.

Administration of pegamotecan

Pegamotecan was supplied by Enzon (Piscataway, NJ) as a sterile white lyophilised powder in 50 ml amber vials. Each 1 ml of reconstituted drug consisted of 60 mg of pegamotecan (1 mg camptothecin) and 9 mg of sodium chloride [United States Pharmacopeia (USP)], in water for injection. The drug was reconstituted by adding 20 ml of 0.9% sodium chloride for injection (USP) to the vial containing 1.2 g of pegamotecan. This stock solution was further diluted with 0.9% saline solution (USP) to a total volume of 250 ml. Pegamotecan was administered at a starting dose of 7,000 mg/m^2 in 250 ml volume over 1 h by intravenous infusion (iv) every 21 days on an outpatient basis. The patient's body surface area was calculated within 72 h prior to each dose. If the calculated volume exceeded 250 ml, pegamotecan was prepared in 500 ml volume which was then infused over 2 h. Treatment was repeated every 21 days until disease progression, intolerable toxicity, patient refusal or investigator decision to discontinue study therapy.

Patients were encouraged to drink at least 3 l of fluid daily during treatment to decrease the risk of haemorrhagic cystitis. Prophylactic treatment of drug-related symptoms was not instituted prior to the first course of treatment. Thereafter, this was considered for patients who experienced drug-related symptoms after evaluation of the relationship to the study medication. If a hypersensitivity reaction occurred, treatment measures were administered as medically appropriate. Patients could subsequently be re-challenged with pegamotecan following prophylactic administration of dexamethasone (8 mg orally or iv every 6 h for four doses prior to pegamotecan treatment), diphenhydramine (50 mg iv), and cimetidine (300 mg iv) or ranitidine (50 mg iv) 30 min before pegamotecan, and by infusing the pegamotecan slowly and increasing the infusion rate gradually to complete the infusion within 2 h.

Administration of subsequent courses of pegamotecan was delayed until the haematological and serum chemistry parameters had recovered to within the limits specified at study entry, and any other treatment-related toxicities (with the exception of alopecia) had resolved to baseline or ≤NCIC-CTC grade 2 or the levels permitted at study entry. Patients were withdrawn from the study if there was a treatment delay of greater than 2 weeks.

The dose of pegamotecan was modified on the second and subsequent cycles of treatment based on the following haematological and non-haematological toxicities. The dose of pegamotecan was reduced by one dose level in the event of grade 4 neutropenia (ANC < 500 μ/l) lasting for >5 days, and/or associated with fever (≥38.5°C), thrombocytopenia <50,000 μ/l, haemoglobin <6.5 g/dl, grade 4 nausea or vomiting despite maximal supportive care, grade 2 haematuria despite optimal fluid loading, or any ≥grade 3 non-haematological toxicities attributable to the study drug. No intra-patient dose escalation was allowed. Up to three dose reductions (to 5,600, 4,800 and 2,400 mg/m^2) were permitted per patient. Patients were withdrawn from the study if there was a requirement for more than three dose reductions (for whatever reason). Dose intensity of pegamotecan was not calculated in this study.

Palliative and supportive care was permitted during the study, and any regular treatment that the patient had been taking within 30 days prior to study entry was continued during the study. Patients were not permitted to receive any other anti-cancer therapy during the study (including hormonal agents and immunotherapy). However, localised radiotherapy was allowed for the purpose of pain relief if other methods of pain control were ineffective. If a patient required localised radiotherapy, pegamotecan was not administered until the patient had completed the radiotherapy treatment and recovered from any acute effects. The prophylactic use of granulocyte colony stimulating factor (G-CSF) was not permitted but could be given therapeutically at the discretion of the investigator, as long as treatment was discontinued 24 h prior to administration of pegamotecan.

Patient assessments

Objective tumour response (i.e. complete and partial response) was determined by CT scan assessments of measurable disease by the RECIST criteria [20]. A pre-treatment CT scan was performed prior to administration of the first cycle of treatment, and subsequent scans were performed after every two cycles of therapy.

Physical examination (including vital signs), assessment of performance status, electrocardiogram (ECG), urinalysis, pregnancy test (when appropriate), full blood count (including differential and platelets), biochemistry profile [urea, electrolytes, creatinine, liver function tests, total protein, serum albumin, lactic dehydrogenase (LDH), glucose], clotting screen, and tumour markers (if appropriate) were performed before the first cycle of treatment.

Physical examination, vital signs, assessment of toxicities, assessment of performance status, full blood count and biochemistry profile were performed prior to each subsequent administration of the study drug. Physical examination, assessment of toxicities, full blood count and biochemistry profile were performed weekly. In addition, the full blood count was repeated daily if febrile neutropenia occurred and the biochemistry profile was determined weekly or twice weekly for patients who developed clinically significant abnormalities of ≥1 CTC grade above their pre-treatment values. The severity of toxicities was recorded using the NCI common toxicity criteria (CTC), version 2.0.

Statistical analyses

All patients who received at least one infusion of pegamotecan were analysed for toxicity, and those who had at least one on-treatment tumour measurement were assessed for response.

The primary efficacy measure for this study was overall tumour response rate. The percentage of patients with complete or partial tumour response was tabulated at each applicable study cycle, at the end of treatment, and during follow-up until disease progression or death. Associated 95% confidence intervals were also displayed. Secondary efficacy measures were time to tumour response, duration of response, time to disease progression and overall survival. These results were presented graphically with Kaplan–Meier curves [21]. Results for these efficacy measures included the number and type of each event, the number of censored observations, and the 13-, 26-, and 52-week survival estimates.

Eastern Cooperative Oncology Group (ECOG) performance status index was defined using a three-level response [positive (a decrease ≥1 point from baseline in two consecutive cycles), stable (no change), and negative (an increase of ≥1 point from baseline in 2 consecutive cycles)], reflecting changes in baseline ECOG performance status [22]. Weight index was defined as a two-level response [positive and negative (an increase or decrease of ≥7% of baseline body weight in two consecutive cycles)] to reflect changes in weight from baseline. These two items were used to derive the Clinical Benefit Assessment (Table 1), which was also a two-category response (positive and negative).

Quality of life (QOL) was summarised using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire [23]. Total scores were categorised into three levels (positive change, no change, and negative change). The distribution of the QOL was tabulated at baseline, for each treatment cycle and at the end of treatment.

The sample size was based on Fleming's two stage design [19] and tested the null hypothesis (H_0) that the true response rate was ≤5% versus the alternative hypothesis (H_a) that the true response rate was at least 20%, with a significance level of 3% and a power of 85%. The first stage of patient enrolment was to include 15 evaluable patients. If one or more patients responded in the first stage then an additional 20 evaluable patients were to be enrolled into a second stage. If fewer than five patients exhibited a response by the end of accrual of the second stage of the study, then the conclusion would be drawn that further investigation of pegamotecan was not warranted for patients with advanced gastric or gastro-oesophageal junction adenocarcinoma.

Results

Patient characteristics

A total of 35 patients with locally advanced inoperable, or metastatic, adenocarcinoma of the stomach or gastro-oesophageal junction were recruited into the study at eight centres (5 in the USA, 3 in the UK) between October 2002 and May 2004 and received at least one cycle of intravenous pegamotecan. Twenty-eight (80%) patients were male and seven (20%) were female. The median age was 63 years (range 36–80 years) and all patients had stage four disease. Seven patients (20%) had received prior chemotherapy for advanced disease, and of these, one had also received prior radiotherapy. Patient characteristics are shown in Table 2.

Table 1 Clinical benefit assessment definitions

Index	Category	Definition
Clinical benefit assessment	Positive	A positive or stable rating for ECOG index and a positive rating for weight index (increases ≥7% in body weight from baseline for 2 consecutive cycles)
	Negative	At least one negative rating for ECOG index or weight index (increase ≤7% in body weight from baseline, stable body weight or decreases in body weight for 2 consecutive cycles)

Table 2 Patient characteristics

Characteristic	Number of patients
Number of evaluable patients	35
Age, median (range), years	63 (36–80)
Sex (male:female)	28:7
Median performance status (ECOG)	1
0	4
1	28
2	3
Previous therapy	
Surgery	10
Palliative chemotherapy only	6
Both chemotherapy and radiotherapy	1
Epirubicin/cisplatin/5-fluorouracil (5-FU)	3
Carboplatin/5-FU	1
5-FU/doxorubicin/mitomycin C	1
Docetaxel/cisplatin	1
Paclitaxel/cisplatin/5-FU	1
Radiotherapy only	0
No prior chemo/radiotherapy	28
Median no. of cycles of pegamotecan (range)	4 (1–11)

All 35 patients were evaluable for toxicity and formed the intention-to-treat study population for all other analyses. Three patients (9%) who did not have an objective tumour assessment due to early clinical disease progression were not evaluable for objective tumour response. Thus 32 patients were evaluable for objective tumour response.

Pegamotecan administration: dose delays and modifications

A total of 137 cycles of pegamotecan were administered to *35* patients (median number of cycles = 4; range 1–11). Thirty (85.7%) patients received at least two doses of study drug and eight (22.8%) patients received at least six cycles of study medication.

Administration of pegamotecan was delayed for 42 cycles (30.7%) in 17 patients (48.6%). This was due to unresolved toxicity in 24 cycles, including grade 3/4 neutropenia, grade 3 leucopenia, grade 3 thrombocytopenia, grade 2 anaemia, grade 1 transaminitis, grade 3 nausea/vomiting, grade 3 bladder pain, grade 3 back pain (disease-related), clinical scheduling (7 cycles), and for a number of other reasons in 11 cycles including urinary frequency, urinary urgency and haematuria, to avoid recurrent dysuria and haematuria, patient convenience, patient request due to a previous episode of haematuria and urinary frequency, and delay of therapy until the results of radiological disease assessment were available. The dose of pegamotecan was reduced on ten occasions in six patients (17.2%). The reasons for the dose reductions were pharmacy error in one patient, grade 2 neutropenia, grade 2 haematuria and grade 3 bladder pain resulting in one dose reduction in another patient, another patient had three dose reductions for grade 4 neutropenia, one patient had two dose reductions for grade 2 urinary pain, with a further patient having two dose reductions for grade 2 urinary frequency. One patient required a dose reduction for grade 1 weight loss. Dose intensity of pegamotecan was not calculated in this study.

Efficacy analyses

Five of the 35 patients enrolled in this study, had a partial response (14.3%, CI 4.8, 30.3).The median time to response was 6.6 weeks (range 5.7–17.7 weeks) and the median duration of response was 18.1 weeks (range 15.4–34.1 weeks). One patient was still classed as achieving a partial response at the time of the last tumour evaluation. Additionally 14 patients (40%) had stable disease with a median time to disease progression of 12.6 weeks (range 11.7–43.9 weeks).

All patients were followed after study discontinuation for disease progression and survival. The overall median time to progression or death was 11.9 weeks (95% CI: 6.6, 13.1, range 3.1–47.3 weeks), and a total of 34 patients (97%) had progressed or died after all follow-up visits had been completed. The median survival time was 38.1 weeks (95% CI: 29.0, 47.3), and the 3-, 6-, and 12-month survival estimates were 82, 68 and 17%, respectively.

One of the patients who achieved stable disease during treatment had a positive Clinical Benefit Assessment. However, 28 (80%) patients had a negative Clinical Benefit Assessment and the remaining six patients (17%) were unevaluable for Clinical Benefit due to missing follow-up data.

Twelve patients (34%) reported an improvement in their QOL assessments from the FACT-G questionnaire at the end of treatment, but 21 patients (60%) reported deterioration in QOL. Two patients did not have follow-up FACT-G questionnaires and so could not be evaluated for change in QOL at the end of treatment.

Toxicity analyses (Table 3)

The most frequently observed haematological toxicity was anaemia, with grade 3 anaemia occurring in eight (22.9%) patients and with no occurrences of grade 4 anaemia. Grade 3 neutropenia occurred in four (11.4%) patients and grade 4 neutropenia in two (5.7%) patients. However, no patients developed febrile neutropenia. Grade 3 and 4 thrombocytopenia occurred in two (5.7%) and 2 (5.7%) patients, respectively. Grade 3 prolongation of the partial thromboplastin time occurred in two (5.7%) patients and grade 1 prolongation occurred in one patient.

Table 3 Grade 3/4 adverse events (NCI-CTC version 2.0)

Grade 3/4 adverse event (NCI/CTC)	Patients ($N = 35$) N (%)	
	Grade 3	Grade 4
Anaemia	8 (22.9)	0
Thrombocytopenia	2 (5.7)	2 (5.7)
Leucopenia	4 (11.4)	1 (2.9)
Neutropenia	4 (11.4)	2 (5.7)
Disseminated intravascular coagulation	0	1 (2.9)
Prolonged thromboplastin time	2 (5.7)	0
Fatigue	8 (22.9)	0
Myalgia	2 (5.7)	0
Anorexia	3 (8.6)	1 (2.9)
Nausea	6 (17.1)	0
Vomiting	4 (11.4)	2 (5.7)
Dysphagia	0	1 (2.9)
Haematemesis	0	1 (2.9)
Dysuria	2 (5.7)	0
Bladder pain	1 (2.9)	0
Urinary frequency	1 (2.9)	0

Worst grade per patient (all cycles)

This resolved with no residual sequelae in all three patients. Grade 4 disseminated intravascular coagulation occurred in one (2.9%) patient.

The most frequently reported non-haematological toxicities were gastrointestinal toxicities which occurred in 33 (94.3%) patients and were generally grade 1 or 2 in intensity. Grade 3/4 toxicities included fatigue in eight (22.9%) patients, nausea in six (17.1%), vomiting in six (17.1%), anorexia in four (11.4%), myalgia in two (5.7%), dysuria in two (5.7%), and dysphagia, haematemesis, bladder pain, and urinary frequency each occurring in one (2.9%) patient. Only one patient (2.9%) developed haemorrhagic cystitis and this patient recovered with no residual effects.

There were no toxic deaths in this study. Three patients died of progressive disease within 30 days of discontinuing study drug, but these events were considered to be unrelated to pegamotecan.

Discussion

DNA normally exists as a supercoiled double helix. During replication, it unwinds with single strands serving as a template for synthesis of new strands. Topoisomerase I causes transient single-strand breaks in the supercoiled DNA duplex resulting in relaxation of supercoiled DNA [24]. As such, topoisomerase I is critical for cell growth and proliferation, and is an important target for the development of anti-cancer drugs.

Camptothecin is a plant alkaloid present in the wood, bark and fruit of the Chinese bush *Camptotheca accuminata* [25]. In 1985, topoisomerase I was found to be the target of camptothecin [26, 27]. The poor solubility of camptothecin precluded the direct parenteral administration to patients. The less water-soluble carboxylate salt of camptothecin was used in the initial phase I clinical trials, and some clinical evidence of activity was observed. However, further clinical development was compromised by its severe and unpredictable toxicity, particularly haemorrhagic cystitis [28, 29].

Subsequently, a number of structural analogues of camptothecin were synthesised with greater water solubility and lower toxicities, including irinotecan and topotecan, which are widely used in clinical oncology practice [30, 31]. Although the clinical roles for these agents are well-established, the overall therapeutic impact of available camptothecin analogues has been modest. One potential strategy to optimise the therapeutic index of camptothecin is to conjugate it to a chemically modified polyethylene glycol (PEG) macromolecule. Pegylated camptothecin is a highly water soluble and stable pro-drug synthesised by conjugating PEG to the 20-hydroxyl group of camptothecin. The conjugate undergoes enzymatic hydrolysis releasing camptothecin into tissues and biological fluids. This has a potential advantage as the prodrug complex locks the camptothecin E ring in its desired active lactone configuration. Selective tumour distribution may also occur as a result of its high molecular weight, enhanced vascular permeation and intrasomal retention. Furthermore, the phase I study of pegylated camptothecin demonstrated a tolerable toxicity profile at the recommended dose, with slow clearance of camptothecin using a convenient single-dosing regimen.

The primary objective of this phase II study was to determine the objective tumour response rate of pegamotecan in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. There were no complete objective responses, but a partial response was observed in 5 of the 35 patients (14.3%) treated in this study with a median duration of response of 18 weeks. Given the small number of patients who achieved a partial response, we did not compare response data for patients with a primary gastric adenocarcinoma with those patients with a primary gastro-oesophageal adenocarcinoma. This response rate is similar to that observed for irinotecan monotherapy [10, 11, 32, 33], and superior to the minimal activity observed with topetecan [12, 13], exatecan [34], and 9-amino-camptothecin [35]. Moreover, seven (20%) of the patients included in the study reported here had received prior chemotherapy for

advanced disease, whereas the studies performed with irinotecan were all in patients with chemo-naive disease. Consequently, it is feasible that this study may have under-estimated the optimal efficacy of pegamotecan in patients with chemo-naive disease. However, given the small number of patients with objective response, we did not consider it meaningful to analyse patients who had received prior chemotherapy separately from those who were chemo-naive. The median time to disease progression was 11.9 weeks (3 months), with a median overall survival of 38.1 weeks (9–10 months), which is superior to the median survival reported for irinotecan in phase II studies of 6.4 and 7.1 months [32, 33], and which is comparable to the median overall survival observed with combination chemotherapy regimes such as ECF, albeit in phase III studies. Clinical Benefit determined by a combination of ECOG performance status and change in body weight, only showed a benefit in one (2.9%) patient. It is likely that both performance status and body weight would be adversely affected by disease progression despite the fact that pegamotecan was reasonably well-tolerated. However, 12 (34.3%) patients reported an improvement in QOL, in keeping with the modest activity of pegamotecan in this disease.

In general, pegamotecan was well-tolerated. Grade 3/4 neutropenia was observed in 17.1% of patients, but there were no episodes of febrile neutropenia and no toxic deaths. In contrast, grade 3/4 neutropenia occurred in 23 and 38.5% of patients in phase II studies with irinotecan [32, 33], with febrile neutropenia occurring in 12.5% of patients in one of these studies [33]. Grade 3/4 non-haematological toxicities of fatigue (22.9%), nausea (17.1%), vomiting (17.1%) and anorexia (11.4%) were similar to those observed with irinotecan [32, 33], although there were no cases of grade 3/4 diarrhoea with pegamotecan. Similarly, urological toxicities were generally mild with haematuria occurring in seven (35%) of patients and microscopic haematuria in another five (14.2%) of patients. Grade 3 toxicity occurred in only three patients, with one case each of bladder pain, urinary frequency and dysuria, and one patient with haemorrhagic cystitis who recovered with no residual effects. There were no grade 4 urological toxicities.

In conclusion, pegamotecan has activity in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma, with an objective response rate of 14.3% and a median overall survival of 38.1 weeks. Grade 3/4 neutropenia, febrile neutropenia and diarrhoea were observed less commonly than with irinotecan, suggesting that pegamotecan could be more easily combined with other active agents such as fluoropyrimidines or platinum analogues if further studies of a topoisomerase inhibitor were considered in this patient population.

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