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ORIGINAL ARTICLE

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A phase II study of Caelyx, liposomal doxorubicin: lack of activity in patients with advanced gastric cancer

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Abstract *Purpose*: A phase II study was designed to assess the efficacy and safety of Caelyx (liposomal doxorubicin) in patients with advanced or metastatic gastric cancer. *Methods*: A total of 25 patients with gastric adenocarcinoma were treated with Caelyx 45 mg/m^2 every 28 days as first-line therapy for advanced disease. Patients were treated until tumour progression or unacceptable toxicity. *Results*: One patient was withdrawn from the study after experiencing a severe infusion reaction. Of the 24 evaluable patients, 1 had a partial response, 7 had stable disease and the others progressed. Side effects, in particular palmar-plantar erythrodysaesthesia and haematological toxicity, were minor. *Conclusions*: We conclude that while this dose and schedule of Caelyx in this patient group is acceptable, further studies with this regimen cannot be recommended due to the lack of antitumour activity seen.

Keywords Caelyx · Liposomal doxorubicin · Phase II · Gastric carcinoma

Introduction

Adenocarcinoma of the stomach remains one of the leading causes of cancer death worldwide [1]. Currently there is no gold standard treatment for advanced gastric cancer. Single-agent anthracyclines have been used in the past with response rates in the range 6–17% [7, 8, 11]. In an attempt to improve activity, combination anthracycline-containing regimens have been studied in the phase III setting. The majority of patients have locally advanced or metastatic disease at the time of diagnosis and while these studies have established the role of chemotherapy in the palliation of symptoms, even with the development of the more intensive combination regimens, median survival remains only 8–11 months [3, 13]. Moreover, toxicity is significant, particularly as these patients are often compromised by a poor functional status.

Liposomal encapsulation of anticancer drugs is a rapidly expanding strategy in the treatment of cancer with the potential of improving the safety and efficacy of cytotoxic agents [5]. There have already been encouraging reports of the use of liposomal doxorubicin (Caelyx, Doxil) in a number of solid tumours [9, 10]. A major toxicity has been palmar-plantar erythrodysaesthesia (PPE), but this has been manageable with administration of 45 mg/m^2 every 4 weeks [2, 10]. We therefore conducted a phase II study using this schedule of Caelyx as first-line treatment for patients with advanced gastric cancer.

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Patients and methods

Eligibility criteria

Patients aged ≥18 years with histologically confirmed locally advanced or metastatic gastric adenocarcinoma (including tumours arising in the gastro-oesophageal junction), and bidimensionally evaluable disease, were enrolled. Prior chemotherapy was not allowed. Other eligibility criteria included performance status (WHO) 0–2, life expectancy of at least 3 months, adequate haematological parameters (haemoglobin ≥9 g/dl, absolute neutrophil count $\geq 1.5\times10^9$/l, and platelets $\geq 100\times10^9$/l), adequate hepatic function (bilirubin less than the upper normal limit (UNL), transaminases less than three times UNL or less than five times UNL in the presence of liver metastases) and adequate renal function (serum creatinine less than UNL). Patients had adequate cardiac function as determined by echocardiography, and no evidence of brain metastases. Patients were offered treatment with either standard combination chemotherapy (ECF or FAM in our institution) or treatment on this study. Toxicities and the method of administration for both schedules were outlined in detail and patients were advised that if they progressed on Caelyx then they would be offered standard therapy. The local ethics committee approved the study and all patients gave written informed consent.

Treatment

Caelyx (Schering-Plough, Welwyn Garden City, UK) 45 mg/m^2 was administered as a 1-h intravenous infusion every 28 days. Prophylactic antiemetics were not routinely administered. Patients were treated until tumour progression or unacceptable toxicity (graded by NCIC CTG Expanded Common Toxicity Criteria). Dose reductions were permitted for side effects that persisted after a 2-week delay, any febrile neutropenia or thrombocytopenic bleeding, or grade 3/4 PPE.

Patient evaluation

Patients underwent a physical examination, full blood count, and biochemistry profile at baseline and prior to each cycle of chemotherapy. Computed tomography of the indicator lesion(s) was obtained at baseline, every second cycle and 4 weeks after documentation of an objective response. Echocardiography was performed at baseline.

Statistical analysis

A Simon two-stage Minimax design was employed to calculate sample size. If fewer than three responses were documented after the enrolment of 25 patients, the likelihood of the response rate being ≥25% was 10% or less. Survival was calculated from the first day of treatment until death.

Results

A total of 25 patients were enrolled (Table 1). One patient was not evaluable for response since he had a severe infusion reaction during the first treatment and came off study. A total of 75 cycles were administered and the median number of cycles given per patient was 2 (range 1–6). Five patients only received one cycle of Caelyx due to their clinical deterioration. Of the 24 evaluable patients, 1 had a partial response, 7 had stable disease and the others progressed. (Seven patients with progressive disease went on to receive second-line chemotherapy.) Median event-free survival was 58 days (range 1–291 days) and median overall survival was 158 days (range 5–415 days). Adverse events were usually mild (Table 2). Of particular interest was a lack of alopecia or neutropenia.

Table 1 Patient characteristics

Age (years)	
Median	70
Range	41–82
Gender	
Male	21
Female	4
WHO performance status	
0	6
1	14
2	5
Stage IV	18
Number of affected sites per patient	
Median	2
Range	1–3
Disease sites	
Lymph nodes	13
Liver	12
Peritoneum	9
Lung	4
Bone	1

Table 2 Adverse events (NCIC CTC grading system)

	Grade 1	Grade 2	Grade 3	Grade 4
Infusion reaction	1	2	2	0
PPE	1	4	0	1
Nausea and vomiting	14	9	1	0
Mucositis	2	2	1	0
Lethargy	6	4	1	1
Thrombocytopenia	2	0	0	0
Anaemia	3	4	0	0

Discussion

Currently there is no consensus as to the optimum chemotherapy regimen for advanced gastric cancer, particularly for poor performance status patients [12]. Most of the regimens in use include anthracycline and are limited by significant toxicity. Liposomal doxorubicin has been found to be efficacious in a number of tumour types including breast and ovarian cancer, and has a superior safety profile compared with conventional doxorubicin. There has been much speculation as to whether liposomal anthracycline may be substituted in the current regimens for gastric cancer. This would clearly be beneficial from the point of view of toxicity, as these patients are often elderly with poor performance status.

This phase II study confirmed that Caelyx is well tolerated when administered to patients with advanced gastric cancer. Unfortunately, five patients clinically deteriorated after the first cycle of Caelyx despite having good performance status at study entry. In our experience this number of treatment failures after one cycle is not surprising when participating in early studies in this patient population. We present our results on an intention to treat basis and therefore the patients were not replaced.

The PPE was manageable and the lack of haematological side effects very encouraging. While all the patients experienced nausea and vomiting, this was usually mild and responded to standard antiemetics. In addition such symptoms in these patients may well have been disease-related. Unfortunately, significant antitumour activity was not seen. It is possible that greater activity would have been seen at the higher dose intensities which have been used in recent trials [4, 6, 9]. However 50 or 60 mg/m^2 every 21 days is associated with significant toxicities, particularly PPE, and these would not be tolerable in patients with inoperable gastric cancer. It is therefore unlikely that Caelyx will have a role in the management of advanced gastric cancer – particularly at the dose and schedule used in the current study.

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References

1. Alexander HR, Kelsen DG, Tepper JC (1997) Cancer of the stomach. In: Devita VT Jr, Hellman S, Rosenberg SA (eds) Cancer: principles and practice of oncology, 5th edn. Lippincott, Philadelphia, pp 1021–1053
2. Baas P, van Meerbeeck J, Groen H, Schouwink H, Burgers S, Daamen S, Giaccone G (2000) Caelyx in malignant mesothelioma: a phase II EORTC study. Ann Oncol 11:697–700
3. Cascinu S, Labianca R, Alessandroni P, Marcellini M, Silva R, Pancera G, Testa E, Martignoni G, Barni S, Frontini F, Zaniboni A, Luporini G, Cellerino R, Catalano G (1997) Intensive weekly chemotherapy for advanced gastric cancer using fluorouracil, cisplatin, epi-doxorubicin, 6S-leucovorin, glutathione, and filgrastim: a report from the Italian Group for the Study of Digestive Tract Cancer. J Clin Oncol 15:3313–3319
4. Ellerhorst JA, Bedikian A, Ring S, Buzaid AC, Eton O, Legha SS (1999) Phase II trial of Doxil for patients with metastatic melanoma refractory to frontline therapy. Oncol Rep 6(5):1097–1099
5. Gabizon A, Martin F (1997) Polyethylene glycol-coated (pegylated) liposomal doxorubicin: rationale for use in solid tumours. Drugs 4:15–21
6. Gordon AN, Granai CO, Rose PG, Hainsworth J, Lopez A, Weissman C, Rosales R, Sharpington T (2000) Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer. J Clin Oncol 18(7):3093–3100
7. Levi JA, Fox RM, Tattersall MH, Woods RL, Thomson D, Gill G (1986) Analysis of a prospectively randomized comparison of doxorubicin versus 5-fluorouracil, doxorubicin and BCNU in advanced gastric cancer: implications for future studies. J Clin Oncol 4:1348–1355
8. Loehrer PJ Sr, Harry D, Chlebowski RT (1994) 5-Fluorouracil versus epirubicin versus 5-fluorouracil plus epirubicin in advanced gastric carcinoma. Invest New Drugs 12(1):57–63
9. Muggia FM, Hainsworth JD, Jeffers S, Miller P, Groshen S, Tan M, Roman L, Uziely B, Muderspach L, Garcia A, Burnett A, Greco FA, Morrow CP, Paradiso LJ, Liang LJ (1997) Phase II study of liposomal doxorubicin in refractory ovarian cancer: anti-tumour activity and toxicity modification by liposomal encapsulation. J Clin Oncol 15:987–993
10. Ranson MR, Carmichael J, O'Byrne K, Stewart S, Smith D, Howell A (1997) Treatment of advanced breast cancer with sterically stabilized liposomal doxorubicin: results of a multicenter phase II trial. J Clin Oncol 15:3185–3191
11. Scarffe JH, Kenny JB, Johnson RJ, Owens SE, Giles GR, Leveson SH, Maley MV (1985) Phase II trial of epirubicin in gastric cancer. Cancer Treat Rep 69(11):1275–1277
12. Vanhoefer U, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Cutsem E, Planker M, Dos Santos JG, Piedbois P, Paillot B, Bodenstein H, Schmoll HJ, Bleiberg H, Nordlinger B, Couvreur ML, Wils JA (2000) Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 18:2648–2657
13. Webb A, Cunningham D, Scarfe JH, Harper P, Norman A, Joffe JK, Hughes M, Mansi J, Findlay M, Hill A, Oates J, Nicolson M, Hickish T, O'Brien M, Iveson T, Watson M, Underhill C, Wardley A, Meehan M (1997) Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin and methotrexate in advanced esophagogastric cancer. J Clin Oncol 15:261–267