PERGAMON

European Journal of Cancer 37 (2001) 1833–1838

European Journal of Cancer

www.ejconline.com

First-line chemotherapy with docetaxel for unresectable or metastatic carcinoma of the biliary tract. A multicentre phase II study

P. Papakostas[a], Ch. Kouroussis[b], N. Androulakis[b], G. Samelis[a], G. Aravantinos[c], K. Kalbakis[b], E. Sarra[b], J. Souglakos[b], S. Kakolyris[b], V. Georgoulias[b,*]

[a]*Oncology Unit, "Hippokratio" General Hospital of Athens, Greece*
[b]*Department of Medical Oncology, University General Hospital of Heraklion, PO Box 1352, 71110 Heraklion, Crete, Greece*
[c]*Third Department of Medical Oncology, "Agii Anargyri" Cancer Hospital of Athens, Greece*

Received 15 November 2000; received in revised form 24 April 2001; accepted 11 June 2001

Abstract

The purpose was to evaluate the efficacy and safety profile of docetaxel as first-line chemotherapy for patients with locally advanced or metastatic biliary tract carcinoma. 25 chemotherapy-naïve patients with unresectable or metastatic biliary tract carcinoma were entered into this phase II trial. Docetaxel was given at the dose of 100 mg/m^2 as a 1-h infusion on day 1, after appropriate premedication with dexamethasone; treatment was repeated every 21 days. Patients were assessed for response every three chemotherapy cycles. 24 patients were evaluable for response and 25 for toxicity. A total of 98 cycles were administered with a median of three cycles/patient. Two complete (CR = 8%) and three partial (PR = 12%) responses were observed (overall response rate: 20%; 95% confidence interval (C.I.) 4–36%); in addition, 6 (24%) patients had stable disease and 14 (58%) progressive disease. With a median follow-up of 8 months, the median duration of response was 4 months, the median time to tumour progression (TTP) was 6 months and the overall median survival was 8 months. The 1-year survival rate was 26%. Grade 3 and 4 granulocytopenia occurred in 36 and 20% of the patients, respectively, and febrile neutropenia was observed in 16% of them; there were no treatment-related deaths. Grade 2–3 fatigue was reported in 24% of patients. These results indicate that docetaxel is an active drug against adenocarcinomas of the biliary tract.

Keywords: Docetaxel; Chemotherapy; Biliary tract carcinoma

1. Introduction

Carcinoma of the biliary tract is a rare disease and its treatment remains a major challenge for both surgeons and medical oncologists. The frequency of these tumours in various Western countries ranges from approximately 2 to 6 per 100 000/year [1].

Within the biliary tract, tumours of the gallbladder are more frequent than tumours of the ductal system. Both tumour types occur preferentially in older patients, with a peak incidence in the fifth to seventh decade. Because of the lack of characteristic early symptoms, curative surgery is rare. Consequently, the course of the disease is usually rapid with a survival time of approximately 6 months [2]. Death is mainly due to gastrointestinal haemorrhage, hepatic failure or progressive cachexia. For patients with locally advanced or metastatic disease, the role of chemotherapy remains a matter of debate and is considered to be largely ineffective.

There are few data in the literature concerning chemotherapy in patients with biliary tract cancer. Most of these studies include small numbers of patients. 5-Fluorouracil (5-FU) and mitomycin-C (Mit-C) are among the most studied agents. Phase II studies have demonstrated that the achieved response rate with 5-FU is usually less than 20% [3]. Mit-C, considered to be active against this disease, resulted in an objective response rate of 10% in an European Organization for

* Corresponding author. Tel.: +30-81-392-747; fax: +30-81-392-802.
E-mail address: georgoul@med.uch.gr (V. Georgoulias).

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00214-3

Research and Treatment of Cancer (EORTC) [4] study. Thus, the need for new, active chemotherapeutic agents is obvious.

Docetaxel is a new antitumour agent belonging to the taxoid family. It is produced by semi-synthesis from a natural noncytotoxic precursor (10-deacetylbaccatin III) extracted from the renewable needle biomass of European yew plants (*Taxus baccata*). Docetaxel disrupts, *in vitro*, the microtubular network, which is essential for cell division, acting as a potent mitotic inhibitor via its novel effects on microtubules. Docetaxel, as monotherapy, has been reported to have very good activity in a variety of tumours such as carcinoma of the breast [5], ovaries [6], lung [7] and stomach [8]. However, there are no published data concerning the activity of docetaxel against biliary tract carcinomas. Therefore, we performed a phase II study to determine the efficacy of docetaxel as first-line chemotherapy in patients with locally advanced or metastatic biliary tract carcinoma.

2. Patients and methods

2.1. Patients

Eligibility criteria included histologically-proven unresectable or metastatic adenocarcinoma of biliary tract, no prior chemotherapy or radiotherapy for metastatic disease, World Health Organization (WHO) performance status 0–2, age 18–75 years, a life expectancy of at least 12 weeks, absence of a second primary malignant tumour (with the exception of a non-melanoma cutaneous carcinoma or cured intraepithelial cervical cancer), no severe organ failure or coronary insufficiency or active infection. Patients were also required to have bidimensionally measurable disease by either ultra-sound or computed tomography (CT) scans. Patients were also required to have an adequate bone marrow (absolute neutrophil count $>1500\times10^6$ cells/l and platelets $>120\times10^9$ cells/l, renal (serum creatinine levels <132.6 μmol/l), and hepatic (serum bilirubin levels <25.65 μmol/l and serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values <4 times the upper normal limits) function.

2.2. Patient evaluation

Pretreatment evaluation included a complete medical history and physical examination; a complete blood cell count (CBC) with a differential and platelet count; a standard biochemical profile as well as measurement of the serum levels of carcinoembryonic antigen (CEA) and CA 19.9; chest X-rays; CT scans of the chest and abdomen. Additional studies were performed if clinically indicated. During treatment, a CBC with a differential and platelet count was performed weekly; in cases of grade 3 or 4 neutropenia, febrile neutropenia or grade 4 thrombocytopenia, the CBC was performed daily until the absolute granulocyte count (ACG) was $\geqslant1000\times10^6$ cells/l and platelets $\geqslant50\times10^9$ cells/l. A detailed medical history was taken and a complete physical examination was performed before each course of treatment to document symptoms of disease and toxicity of chemotherapy. Biochemical tests, electrocardiogram and chest X-rays were performed every 3 weeks. A clinical neurological evaluation was performed in each cycle and motor and sensory nerve conduction velocity tests were performed in cases of grade 3 or 4 neurotoxicity. Lesions were evaluated at each cycle if they were assessable by physical examination or chest X-rays. In all patients response to treatment was assessed by physical examination, if appropriate, and/or abdomen imaging procedures (CT scans or ultrasound) every three chemotherapy cycles.

2.3. Treatment

Docetaxel was administered intravenously (i.v.) at a dose of 100 mg/m^2 as a 1-h infusion on day 1 and treatment was repeated every 3 weeks. All patients were premedicated with i.v. dexamethasone 8 mg, 12 h and 6 h before the administration of docetaxel in order to reduce the risk of hypersensitivity reactions and fluid retention syndrome. Moreover, dexamethasone (4 mg orally, every 12 h for four doses) was given after chemotherapy. Antiemetics and cimethidine were also given. Dose adjustment was performed according to toxicity. A 25% dose reduction of docetaxel was required in cases of grade 4 neutropenia or febrile neutropenia. Moreover, the dose of docetaxel was reduced by 25% in all cases of grade 3 and 4 non-haematological toxicity. Patients presenting serum levels of alkaline phosphatase or γ-glutamyl transpeptidase (γGT) more than 3 times the upper normal levels, received a reduced (75 mg/m^2) dose of docetaxel.

2.4. Treatment evaluation

All responses were defined according to WHO guidelines as follows: Complete Responses (CR): disappearance of all measurable or evaluable disease, with no new lesions; Partial Response (PR): 50% reduction in the sum of the products of the largest perpendicular diameters of all measurable disease sites with no new lesions; Stable Disease (SD): less than 50% reduction or an increase of less than 25% of measurable disease according to the previous method, with no new lesions; Progressive Disease (PD): more than 25% increase in any measurable disease site or the appearance of new lesions. All radiological data were reviewed by a panel of two independent radiologists. All toxicities were graded according to the WHO criteria.

2.5. Statistical design

The study was a two-step multicentre phase II trial. If one objective response occurred during the first 15 enrolled patients, 15 additional patients were enrolled. The primary end-points were response to treatment and toxicity, whereas overall survival was considered as a secondary end-point. The duration of response was calculated from the day of the first demonstration of response to disease progression; the time to tumour progression (TTP) was estimated from study entry until the documented progression of the disease and the overall survival was measured from study entry to death. Actuarial probability of survival and the median TTP were estimated by the method of Kaplan–Meier; 95% confidence intervals (95% C.I.) for response rate were calculated using methods for exact binomial confidence intervals. Comparison of variables was performed using the Log-rank test.

3. Results

3.1. Patients' characteristics

Between April 1996 and May 1999, 25 patients were enrolled onto this multicentre phase II study. The study was closed before the enrolment of the scheduled 30 patients because of the very low accrual rate. Patient's characteristics are listed in Table 1. There were 14 (56%) men and 11 (44%) women with a median age of 66 years (range 47–75 years); the median WHO performance status was 1 (range 0–2). The primary cancer sites were the gallbladder for 16 (64%) patients, the bile ducts for 5 (20%) and the ampulla of Vater for 4 (16%) patients. Assessable sites of disease were mainly the gallbladder (8 patients), the liver (19 patients), the lymph nodes (6 patients), the lungs (2 patients) and the peritoneum (4 patients). 3 patients had malignant ascitis and 1 malignant pleuritis, but these tumour localisations were not considered as measurable lesions. The number of metastatic sites was one for 13 (52%), two for 10 (40%) and three for 2 (8%) of the patients.

Table 1
Patients characteristics

Characteristic	No of patients (%)
Patients treated	25
Sex	
Male	14 (56)
Female	11 (44)
Age (years)	
Median (range)	66 (47–75)
WHO performance status	
0	9 (36)
1	10 (40)
2	6 (24)
Primary cancer site	
Gallbladder	16 (64)
Bile ducts	5 (20)
Ampulla of Vater	4 (16)
Sites of disease	
Gallbladder	8 (32)
Liver	19 (76)
Lymph nodes	6 (24)
Lungs	2 (8)
Peritoneum	4 (16)
Ampulla of Vater	1 (4)
Pleura	1 (4)
Other	7 (28)
No of metastatic sites	
1	13 (52)
2	10 (40)
3	2 (8)

WHO, World Health Organization.

3.2. Efficacy and survival

24 patients were assessable for response. One patient refused further treatment after the first cycle of chemotherapy. In an intention-to-treat analysis, two complete (8%) and three partial (12%) responses were observed for an overall response rate of 20% (95% C.I. 4.32–35.68%). 6 patients had stable disease (24%) and 14 progressive disease (56%). One of the partial responders suffered from an ampulloma. One patient with SD who presented multiple pulmonary lesions and 1 patient with PD who presented multiple hepatic lesions were evaluated with only chest X-rays and liver ultrasound, respectively. Responses, according to the sites of disease, were noted in the gallbladder (two of 7; 25%), liver (four of 19; 21%), lymph nodes (one of 6; 17%) and other sites, including 1 case of ampulla of vater and 1 case of pleural mass (three of 9; 33%) (Table 2). With a median follow-up of 8 months (range: 1.5–42 months), the median duration of response was 4 months (range: 3.5–19 months), the median TTP was 6 months (range: 1.5–24 months) and the overall median survival was 8

Table 2
Response to docetaxel by metastatic site

	No. of patients (%)				
Metastatic sites	*n*	CR	PR	SD	PD
Gallbladder	7	1 (14)	1 (14)	2 (19)	3 (43)
Liver	19	2 (11)	2 (11)	4 (21)	11 (58)
Lymph nodes	6	1 (17)	–	2 (33)	3 (50)
Lungs	2	–	1 (50)	–	1 (50)
Peritoneum	4	–	–	2 (50)	2 (50)
Others	9	1 (11)	2 (22)	2 (22)	4 (45)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

months (range: 1.5–42 months; 95% CI: 6.45–9.55). The 1-year survival probability was 26% (Fig. 1). One of the patients with a PR had an ampulloma; the duration of response in this particular patient was 19 months, whilst it was 4 months (range: 1.5–15 months) in the remaining responders. Moreover, the median survival of the 4 patients with ampullomas was 9 months (range: 2–42 months), compared with 7.5 months (range: 1.5–27.5 months) in the remaining patients.

3.3. Compliance with the treatment and toxicity

All 25 patients were evaluated for toxicity. A total of 98 cycles of therapy were delivered with a median of 3 cycles/patient (range: 1–9 cycles/patient). The median dose of docetaxel administered per cycle was 100 mg/m^2 (range: 66–100 mg/m^2) corresponding to the 100% of the protocol planned dose (mean cumulative dose±standard deviation (S.D.): 608±316 mg); the median interval between cycles was 21 days (range: 21–28 days), (mean±S.D.: 21.1±3.5 days). Eight (8%) cycles were delayed (mean±S.D.: 11±6 days); in addition, the doses were reduced because of grade 3 or 4 toxicity in 4 (4%) other cycles. No toxic deaths were reported. The incidence of the main side-effects, determined as the maximum grade seen per patient, is listed in Table 3. No treatment discontinuation was reported because of adverse events. Grade 3 and 4 granulocytopenia was the most frequent severe side-effect and occurred in 14 (56%) patients (36% of patients presented with grade 3 and 20% with grade 4 granulocytopenia). Overall, 22 (22%) of the cycles were complicated with grade 3 or 4 granulocytopenia; 16 neutropenic episodes occurred during the first two cycles, whilst the other six occurred during the third and fourth cycles. Febrile neutropenia occurred in 4 patients (16%); all patients were hospitalised (median duration of hospitalisation: 5 days (range: 4–7 days)) and were uneventfully treated with i.v. antibiotics. Granulocyte colony-stimulating factor (rhG-CSF) was administered in 17% of the treatment cycles because of granulocytopenia and in 53% of cycles prophylactically. The incidence of grade 3 and 4 granulocytopenia was different among patients who presented normal or increased serum levels of ALP and/or γ-GT at baseline. Indeed, 11 (79%) out of 14 patients who developed grade 3–4 granulocytopenia had increased levels of ALP and/or γ-GT (median 2-fold increase; range: 1.5–4.5). In 13 of these patients, no prophylactic rhG-CSF had been administered. No grade 3 or 4 anaemia or thrombocytopenia were seen. The non-haematological toxicities were mild to moderate (Table 3) and 6 (24%) patients experienced grade 2–3 fatigue.

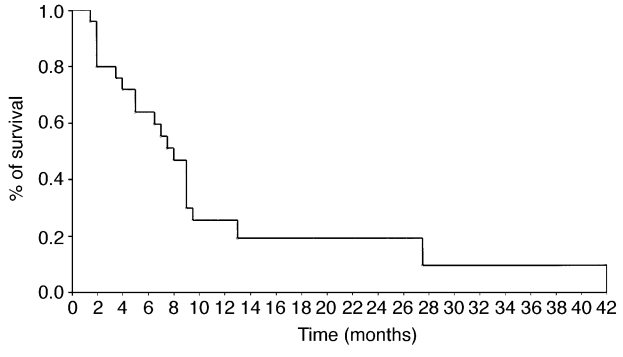

Fig. 1. Actuarial Kaplan–Meier survival of patients with biliary tract carcinoma treated with single-agent docetaxel.

4. Discussion

Adenocarcinoma of the biliary tract is a relatively rare tumour in which surgery offers the only hope for cure. The role of chemotherapy remains a matter of debate. Owing to the relative rarity of the disease and to the fact that the lesions are difficult to measure, only a few chemotherapy trials have been performed in advanced biliary cancer and these have included small numbers of patients. Most previous studies have involved 5-FU and Mit-C treatment. For 5-FU, the reported response rates are low and usually below 20% [3,9]. Furthermore, Mit-C, considered by some to be an active drug for the treatment of this disease, resulted in an objective response rate of 10% in an EORTC study [4]. Cisplatin has also been tested in the biliary tract and was found to have a marginal activity (response rate $\leqslant$8%) [10]. Gemcitabine, a new chemotherapeutic agent, showed no activity in a small phase II trial (response rate = 0%) [11]. Therefore, the results of single agent therapy have been disappointing, with most compounds being rather ineffective in terms of objective responses to treatment.

Table 3
Toxicity profile of single-agent docetaxel in patients with a carcinoma of the biliary tract

	WHO grade			
	No. of patients (%)			
Toxicity	1	2	3	4
Granulocytes	2 (8)	1 (4)	9 (36)	5 (20)
Haemoglobin	13 (52)	6 (24)	–	–
Platelets	3 (12)	–	–	–
Nausea-vomiting	5 (20)	6 (24)	–	–
Diarrhoea	4 (16)	2 (8)	–	–
Mucositis	2 (8)	–	–	–
Neurotoxicity	5 (20)	1 (4)	–	–
Fatigue	2 (8)	4 (16)	2 (8)	–
Rash	2 (8)	–	–	–
Oedema	2 (8)	–	–	–
Alopecia	14 (56)	9 (36)	–	–

WHO, World Health Organization.

Various combination regimens have also been tested for the treatment of advanced biliary cancer in phase II studies, but response rates in excess of 30% have been difficult to achieve [12–15] which indicates the urgent need for the evaluation of new chemotherapeutic agents.

Docetaxel is an antineoplastic agent belonging to the taxoid family and has been found to have promising efficacy in a variety of tumours such as breast [5], ovarian [6], lung [7] and gastric [8] carcinoma. However, to the best of our knowledge, there is no published data evaluating the activity of docetaxel in patients with biliary tract carcinomas. In this phase II study, we investigated the activity of docetaxel, as first-line treatment, in patients with unresectable locally advanced or metastatic biliary tract carcinomas. The dose of 100 mg/m^2, every 3 weeks, is considered to be the standard for single agent docetaxel. An objective response rate of 20% (CR = 8% and PR = 12%) was achieved, and 24% of the patients had stable disease. The median duration of response was 4 months. Moreover, the observed median overall survival of 8 months and the 1-year survival rate of 26% are encouraging. However, important differences were observed between patients with ampullomas and those with tumours of the gallbladder and biliary ducts. Indeed, the median duration of response in one of the responding patients with carcinoma of the ampulla of Vater was 19 months being the median survival for all the fair patients with ampullomas was 9 months. In contrast, the median duration of response in the remaining patients was 4 months and the median survival was 7.5 months. This observation further underlines the better prognosis of ampullomas which seem to be more chemosensitive than carcinomas of the gallbladder and biliary ducts. The 20% objective response rate (with a CR = 8%) seen in our study is superior to the response rate obtained with the single agents 5-FU [3,9], Mit-C [4], cisplatin [10] or gemcitabine [11], whilst the median survival of the patients appears to be comparable to that of combination chemotherapy [12,15,16]. This efficacy following docetaxel administration as first-line treatment is in contrast with the results obtained with paclitaxel treatment. Indeed, in a phase II trial, where paclitaxel was given to 15 patients with unresectable or metastatic carcinoma of the biliary tract at the dose of 170–180 mg/m^2 every 21 days; after 43 cycles of treatment, no objective responses were noted [17].

In our study, the compliance with the treatment was good, since the median dose intensity was 100% of the protocol planned dose and the drug could be delivered on time (every 21 days). The number of delayed cycles was low (8%), with only four cycles requiring dose reduction. In addition, no treatment-related deaths were observed and chemotherapy was not interrupted because of adverse events. The toxicity profile of docetaxel, evaluated in all patients and all cycles, was acceptable and similar to that reported in other docetaxel phase II studies. Indeed, the main toxicity was grade 3 and 4 granulocytopenia occurring in 14 (56%) of the patients, but febrile neutropenia was noted in only 4 (16%) of the patients. It is interesting to note that severe grade 3 and 4 granulocytopenia occurred mainly in patients with increased serum levels of ALP and/or γ-GT. This finding is in agreement with previous studies showing an impaired toxicity profile of docetaxel in patients with intra-hepatic biliary tract obstruction or/and hepatic insufficiency allowing a decreased docetaxel clearance [18]. The increased incidence of severe neutropenia in such patients was the reason for the prophylactic use of rhG-CSF in 53% of the delivered cycles. This prophylactic use of rhG-CSF may be responsible for the relatively low incidence of severe neutropenia, febrile neutropenia and the good compliance with the treatment. The non-haematological toxicities were mild to moderate.

In conclusion, the results of this phase II study seem to indicate that docetaxel is an active and relatively well tolerated agent against carcinomas of the biliary tract. Moreover, this trial may serve as the basis for new trials designed to test the activity of docetaxel in combination with other effective drugs in order to improve the survival of these poor prognosis patients.

Acknowledgements

This work was partly supported by the Gretan Association for Biomedical Research (CABR); Dr E. Sarra and J. Souglakos are recipients of a CABR clinical fellowship.

References

1. Parkin DM, Whelan SL, Ferlay J, *et al*, eds., *Cancer Incidence in Five Continents*. Lyon, IARC, 1997.
2. Altaee MY, Johnoson PJ, Farrant JM, *et al*. Etiologic and clinical characteristics of peripheral and hilar cholangiocarcinoma. *Cancer* 1991, **68**, 2051–2055.
3. Davis HJ, Ramized G, Ansfield FJ. Adenocarcinomas of stomach, pancreas, liver and biliary tracts: survival of 328 patients treated with fluoropyrimidine therapy. *Cancer* 1974, **33**, 193–197.
4. Taal BG, Audisio RA, Blieiberg H, *et al*. Phase II trial of mitomycin C (MMC) in advanced gallbladder and biliary tree carcinoma. An EORTC Gastrointestinal Tract Cancer Cooperative group Study. *Ann Oncol* 1993, **4**, 607–609.
5. Chan S, Friedrichs K, Noel D, *et al*. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1999, **17**, 2341–2354.
6. Kaye SB, Piccart M, Aapro M, *et al*. Phase II trials of docetaxel (Taxotere) in advanced ovarian cancer—an updated overview. *Eur J Cancer* 1997, **33**, 2167–2170.
7. Fossella FV. Overview of docetaxel (Taxotere) in the treatment of non-small-cell lung cancer. *Semin Oncol* 1999, **26**(Suppl. 11), 4–8.
8. Roth AD, Maibach R, Martinelli G, *et al*. Docetaxel (taxotere)-cisplatin (TC): an effective drug combination in gastric cancer.

Swiss Group for Clinical Cancer Research (SAKK) and the European Institute of Oncology (EIO). *Ann Oncol* 2000, **11**, 301–306.
9. Falkson G, MacIntyre JM, Moertel CG. Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer. *Cancer* 1984, **54**, 965–969.
10. Okada S, Ishii H, Nose H, *et al*. A phase II study of cisplatin in patients with biliary tract carcinoma. *Oncology* 1994, **51**, 515–517.
11. Mezger J, Sauerbruch T, Ko Y, *et al*. Phase II trial of gemcitabine (GEM) in biliary tract cancers (BTC). *Proc Am Soc Clin Oncol* 1997, **297** (abstr 1059).
12. Harvey JH, Simth FP, Schein PS. 5-Fluorouracil, mitomycin and doxorubicin (FAM) in carcinoma of the biliary tract. *J Clin Oncol* 1984, **2**, 1245–1248.
13. Kajanti M, Pyrhonen S. Epirubicin-sequential methotrexate biliary system. A phase II study. *Am J Clin Oncol* 1994, **17**, 223–226.
14. Patt YZ, Jones DV, Hoque A, *et al*. Phase II trial of intravenous fluorouracil and subcutaneous interferon alpha-2b for biliary tract cancer. *J Clin Oncol* 1996, **14**, 2311–2315.
15. Okada S, Okusaka T, Ishii H, *et al*. Phase II trial of cisplatin, epirubicin and continious infusion 5-fluorouracil (5-FU) (CEF therapy) for advanced gallbladder cancer. *Proc Am Soc Clin Oncol* 1997, **301** (abstr 1072).
16. Di Lauro L, Carpano S, Capomolla E, *et al*. Cisplatin, epirubicin and fluorouracil (PEF) for advanced biliary tract carcinoma. *Proc Am Soc Clin Oncol*, 1997, **297** (abstr 1021).
17. Jones DV, Lozano R, Hoque A, *et al*. Phase II study of paclitaxel therapy for unresectable biliary tree carcinoma. *J Clin Oncol* 1996, **14**, 2306–2310.
18. Bouker SD, Ravdin P, Aylesworth C, *et al*. A phase I and pharmacokinetic study of docetaxel in patients with liver metastases with or without impaired liver function due to malignances. *Ann Oncol* 1998, **102** (Suppl. 2) 102 (abstr).