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ORIGINAL ARTICLE

Multicenter phase-II trial of irinotecan plus oxaliplatin [IROX regimen] in patients with poor-prognosis cancer of unknown primary: a hellenic cooperative oncology group study

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Abstract
Background Cancer of unknown primary (CUP) lacks established therapy although it affects 3% of cancer patients. We evaluated the irinotecan–oxaliplatin combination (IROX regimen) in previously untreated patients with non-favorable subsets of unknown primary carcinomas.
Methods This was a multicenter phase-II trial. Protocol treatment consisted of oxaliplatin 80 mg/m^2 followed by irinotecan 160 mg/m^2 administered every 3 weeks. The primary end points were response rate and toxicity, and secondary end points were time to progression and survival.
Results Forty-seven patients with liver, bone or multiple visceral metastases entered into the trial and received a median 6 chemotherapy cycles (1–11). The regimen was very well tolerated with one febrile neutropenia case and six cases with diarrhea grade 3 (16%). In intent-to-treat analysis the tumor response rate was 13% (95% CI = 4.8–25.7%) and 12 patients (27%, 95%CI 13.9–40.4%) had at least 4 months' duration of disease stabilization. The median time to progression was 2.7 months and the median survival was 9.5 months, with 40% of patients alive at 1 year.
Conclusions The IROX regimen demonstrated similar efficacy and a favorable toxicity profile compared to other more toxic chemotherapy combinations in patients with poor-prognosis CUP.

Keywords Unknown-primary-carcinoma · Chemotherapy · Oxaliplatin · Irinotecan · Trial · Phase-II

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Introduction

Patients diagnosed with poor-prognosis cancer of unknown primary site (CUP) have limited therapeutic options available, as no standard therapy exists for this clinical entity, which is not infrequently encountered in clinical oncology practice as it affects approximately 3% of cancer patients [1,2]. CUP diagnosis covers a highly heterogeneous group of metastatic tumors in which a site of origin cannot be clinically assigned at the time of diagnosis [3]. Although advances have been made over the past few years in the treatment of certain favorable clinicopathologic subsets, for the majority of CUP patients who usually present with

widely disseminated visceral metastases most tested chemotherapy combinations have produced marginal clinical benefits [4–7]. Nevertheless, repeated failures have continued to drive clinical research toward exploring new regimens and treatment approaches, with the hope of improving the clinical outcome in this patient population.

This trial is the third of a series of clinical studies conducted over a 10-year period by the Hellenic Cooperative Oncology Group [HeCOG] in cancer of unknown primary [5,8]. In our previous phase-II trial the carboplatin–paclitaxel combination was found effective in patients with favorable CUP subsets but failed to demonstrate adequate clinical benefit in patients with liver, bone, or multiple organ involvement [5]. Considering the results of that study and also similar findings reported by other investigators we decided to proceed with separate trials for the favorable and the non-favorable CUP sub-types [9–11].

This study reports the results of the irinotecan–oxaliplatin combination tested in patients with poor-prognosis CUP. We chose these two drugs on the basis of clinical activity and their pharmacological characteristics. Irinotecan, an inhibitor of topoisomerase I, which binds to the topoisomerase I/DNA complex and prevents relegation of single-strand DNA breaks, constitutes an ideal partner in combination with oxaliplatin, a 1,2 diaminocyclohexane platinum salt with increased inherent ability to circumvent tumor resistance [12–14]. We considered that the combination of two compounds with complementary mechanisms of action, preclinical indications of synergy and lack of cross-resistance, formed a rational basis offering promise for activity against these hard-to-treat tumors [15,16]. In clinical experience both drugs have shown activity against a variety of cancer types, including histotypes known to represent the most common occult primaries and moreover, their combination has been shown to be tolerated with manageable toxicity [17–20].

Patients and methods

Study design

This non-randomized multicenter phase-II study was activated in May 2000 and accrued 47 patients with a diagnosis of poor-risk cancer of unknown primary site over a 28-month period. The study was sponsored by the Hellenic Cooperative Oncology Group (HeCOG, code number HE12A.00) and was conducted in ten centers of the HeCOG network. The procedures followed were in accordance with the Helsinki Declaration (1964, amended in 1975, 1983, 1989, 1996 and 2000) of the World Medical Association. The trial protocol and patient informed consent were approved by institutional review boards and the ethics committee of the Ioannina University Hospital. All patients were registered at the HeCOG central office within 7 days prior to treatment initiation.

Eligibility

This trial was open to adult patients with histological diagnosis of unknown primary carcinoma presenting with liver, bone or multi-visceral metastases and unidimensionally measurable disease assessed by radiological studies, within 14 days of enrolment, a performance status 0, 1 or 2 of the World Health Organisation scale and adequate organ function defined by the following criteria: serum aspartate transaminase (AST) and serum alanine transaminase (ALT) $<2.5 \times$ the institutional upper limits of normal range (ULN), or AST and ALT $<5 \times$ ULN in the presence of liver metastases, total serum bilirubin $<1.5 \times$ ULN, absolute neutrophil count (ANC) > 1,500/μl, platelet >100,000/μl, haemoglobin >8.0 g/dl and serum creatinine $<1.5 \times$ ULN. Exclusion criteria to this trial were: locally treatable disease, central nervous system metastases not controlled with previous radiation therapy, female subjects with peritoneal or axillary lymph node carcinoma of unknown primary site, male subjects with elevated serum levels of prostate-specific antigen, β-human chorionic gonadotropin or alpha-fetoprotein, previous chemotherapy, concomitant uncontrolled, non-malignant disease (heart failure or uncontrolled coronary disease, uncontrolled diabetes mellitus, active infection, chronic diarrhoea or unresolved bowel obstruction/sub-obstruction), other malignancies and pre-existing peripheral neuropathy. Eligible patients willing to be treated in this trial were required to have signed an informed consent indicating that the patient had been informed of all the aspects of the trial and had voluntarily accepted the treatment protocol.

Disease definition

Patients were considered to have carcinoma of unknown primary site if the following procedures failed to identify the site of origin of metastatic carcinoma: thorough medical history and physical examination (including head and neck, rectal, pelvic and breast examination), basic blood and biochemistry survey, urinalysis, fecal occult blood test, computed tomography scans of thorax, abdomen and pelvis, and directed imaging studies and endoscopies according to symptoms, signs and findings. Immunohistochemical evaluation for neuroendocrine markers, leukocyte common antigen, vimentin, HMB-45, β-human chorionic gonadotropin (βHCG) and alpha-fetoprotein (AFP) were required in cases of poorly differentiated carcinomas and additional immunohistochemical markers such as cytokeratins 7 and 20 and estrogen receptors were utilized on an individual

basis. Male patients were required to have tested negative for serum β-human chorionic gonadotropin (βHCG), alpha-fetoprotein (AFP) and prostate specific antigen (PSA). Favorable subsets such as young and middle-aged adults with predominantly nodal metastases and females with peritoneal adenocarcinoma of a serous histological type and female patients with adenocarcinoma involving only axillary lymph nodes were excluded from this trial.

Treatment protocol

All patients received treatment according to the following schema: oxaliplatin (L-OHP, Sanofi-Winthrop, later Aventis, France) 80 mg/m^2 diluted in 500 D_5W was infused over 60 min followed by irinotecan (CPT11, Rhône-Poulenc Rorer, France, later Pfizer, SW) 180 mg/m^2 diluted in 250 NS also infused over 60 min. Based on available phase-I data [21] we used relatively low doses for this trial (80–180 instead of the recommended 85–200) in the interest of safety because of the relatively poor physical condition of target population. Courses were scheduled to be repeated at 21-day cycles in the absence of unacceptable toxicity. All patients received prophylactic intravenous anti-HT3 antiemetic medication prior to oxaliplatin and subcutaneous 0.5 mg atropine prior to irinotecan for the irinotecan-related cholinergic syndrome. Re-treatment criteria included an absolute neutrophil count of at least 1,500/μl, a platelet count of at least 100,000/μl and resolution of any treatment-related non-hematologic toxicities (excluding alopecia) to grade 1 or better. Appropriate supportive care, including blood supporting growth factors, antibiotics and antidiarrheal medications for delayed diarrhea (onset >24 h from the end of irinotecan infusion) was provided as necessary during therapy. Prophylactic G-CSF could be administered for 3 days prior to and 3 days post the expected nadir time in patients having experienced an episode of grade-4 neutropenia or febrile neutropenia. Epoetin was allowed for Hb lesser then 10 g/dl. No prophylaxis was provided for delayed diarrhea but on occurrence of first loose stool, patients would start on loperamide 4-mg orally every 8 h for 48 h. Treatment duration in the absence of severe toxicity depended on the tumor response to therapy. Patients without objective tumor progression could continue treatment to a maximum of 12 cycles or until evidence of disease progression, unacceptable toxicity, or patient's wish.

Dose modification and re-treatment criteria

Dose modifications were based on blood cell counts taken on the day of planned treatment, and for febrile neutropenia or organ-specific toxicity occurring at any time during therapy. For re-treatment, it was necessary for any toxicity to have settled down to grade 1 or better. Treatment delay of a maximum 14 days was allowed for recovery from toxicity. For febrile neutropenia and haematological toxicity grade 2 and higher. occurring on day 21, and organ-specific toxicity occurring at any time, doses were reduced at predefined fractions. Patients were given instructions to make use of loperamide for late diarrhea events. Patients would be hospitalized for grades 3–4 diarrhea and fever, or diarrhea associated with signs of dehydration or worsening of performance status. Doses were not to be re-escalated on improvement or resolution of toxicity, whenever dose reductions were applied. However, for patients not experiencing toxicity, the treatment could be given every 2 weeks at the discretion of the treating physician.

Evaluations

Before each cycle, patients were examined for toxicity and had full blood counts and chemistry analysis performed. The National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0 was applied for grading of toxicity. After the second cycle of treatment, patients were evaluated for tumor response to treatment by using the Response Evaluation Criteria in Solid Tumors (RECIST) method [22]. For evaluation of anti-tumor activity $\geq$1 and $\leq$10 measurable lesions were identified as target lesions in each patient. Target lesions were reassessed by the same imaging techniques used for baseline measurements in each case and were repeated at the end of every second cycle. Other evaluations included assessment of WHO PS and symptoms reported. Post-treatment discontinuation patients were followed quarterly for tumor status and survival.

Statistical analysis

The primary objective of this trial was to determine the tumor response rate in patients with poor prognosis cancer of unknown primary when treated with the irinotecan plus oxaliplatin combination. Secondary end-points were toxicity of IROX regimen in this group of patients, time to progression and survival.

The objective response rate was calculated on intent-to-treat basis among all eligible patients with measurable disease who started on treatment. The trial was structured on the basis that the smallest objective response rate that would warrant further investigation in this patient population was 20% and a response rate below 10% would be of no interest. A total of 46 patients were to be accrued following Simon's two stage min max design, with the trial proceeding to full accrual if objective responses were seen in at least three among the first 15 patients registered. Toxicity and antitumor activity were both analyzed for the intention-to-treat population. Survival was estimated from the date of treatment initiation to the date of last follow-up

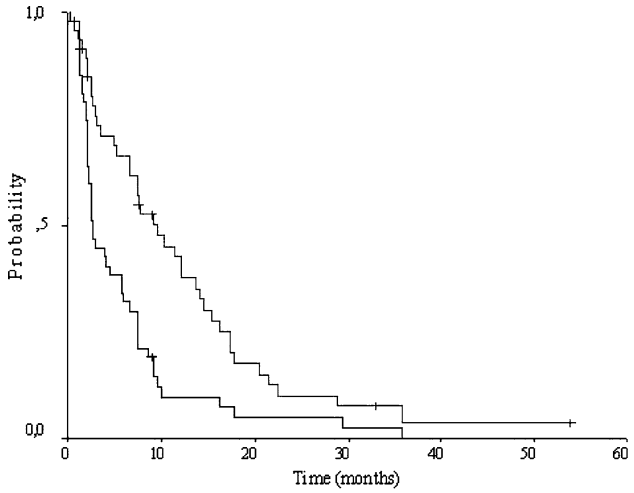

Fig. 1 Kaplan–Meier curves for patients' survival (*dim line*) and time to disease progression (*dark line*)

or until the patient's death. Time to disease progression (TTP) was defined as the number of months from administration of first study medication to first documentation of disease progression. However, deaths attributed to disease-related factors in patients not having previous documentation of disease progression were considered to be events in the estimation of TTP. The Kaplan–Meier method was used to estimate TTP, median follow up, and survival. Exact binomial confidence intervals (CI) were used to determine the 95% upper and lower confidence limits of the response rate. The database was locked in January 2006 and analyses were carried out using SPSS version 10 (SPSS Inc., Chicago, IL, USA).

Results

Patient population

The study characteristics are depicted in Table 1. Forty-seven patients including 33 males and 14 females were enrolled in the study. The median age was 60 years (range 30–70 years). Adenocarcinoma was by far the most frequent histological diagnosis (88% of cases) with a small proportion diagnosed as undifferentiated (6%) or undefined (6%) carcinomas. Among metastatic sites involved the liver was the organ most commonly affected (57%) followed in rank by lung, bone and lymph nodes. Regarding metastatic spread, in 12 patients (26%) liver was the only metastatic site, 29 patients (62%) had more than two, and 12 patients (26%) more than three organ sites involved. Gastrointestinal (GI) endoscopies performed at initial evaluation work-up in seven patients with clinical suspicion of a GI primary tumor were all negative: colonoscopy in six (11%) patients and upper GI endoscopy in two (4%) patients.

Table 1 Study characteristics

	Median (range)	*n*	%
Gender			
Male		33	70
Female		14	30
Age	59.5 (30–70)		
PS	1 (0–2)		
0		16	34
1		20	43
2		11	23
Tumor histology			
Adenocarcinoma well and moderately differentiated		19	40
Adenocarcinoma poorly differentiated		22	48
Undifferentiated carcinoma		3	6
Undefined (cytological diagnosis)		3	6
Organs involved			
Liver		27	57
Lung		18	38
Bones		13	28
Lymph nodes		13	28
Abdomen		9	19
Skin		4	9
Adrenal		1	2
Other		6	13
Metastatic spread			
1 Organ involved[a]		18	38
2 Organs involved		17	36
>3 Organs involved		12	26

[a] Those were cases with multiple metastases in liver (12), bone (2), adbomen (2 males) and lung (2)

Treatment delivered

Treatment administration data is given in Table 2. A total of 209 treatment courses were delivered, with a median six cycles administered per patient (range 1–11). The relative dose intensity of the two drugs was very close to the planned. Nineteen patients (40%) completed six treatment cycles and 60% discontinued treatment for a number of reasons but the majority was because of disease progression. Because of lack of toxicity in the first cycle five patients received therapy every 2 weeks.

Toxicity

Toxicity was evaluated in all patients for all courses. Toxicities with at least one event of Grade 2 recorded are shown in Table 3. Neutropenia grades 3 and 4 were insignificant in this trial. There was only one case of febrile neutropenia and seven cases (16%) of uncomplicated grades 3–4

neutropenia/leucopenia which resolved after one week. Thrombocytopenia and anemia were not noticed. Regarding non-hematological toxicity only grade-3 toxicities were experienced by 24% of treated patients. Those included diarrhea (16% of patients, grade 3) and occasionally peripheral neuropathy, vomiting, fatigue and abdominal pain (2% each). Two patients (7%) were withdrawn from therapy because of grade-3 diarrhea. There was no toxic death in this trial.

Table 2 Treatment administered [total treatment courses delivered = 209]

	Median (range)	*N*	%
Patients completed six cycles		19	40
Discontinued treatment		28	60
Discontinuation reasons[a]			
Death		3	11
Progression		18	64
Toxicity (grade-3 diarrhea)		2	7
Doctor's decision		1	4
Patient's decision		4	14
Treatment courses per patient	6 (1–11)		
Doses administered			
Irinotecan dose (mg/m^2/weeks)	55 (38–80)		
RDI[b] (irinotecan)	0.92 (0.64–1.34)		
Oxaliplatin dose (mg/m^2/weeks)	26 (19–44)		
RDI[b] (oxaliplatin)	0.97 (0.72–1.64)		

[a] Percentages are calculated among non-completers

[b] RDI relative dose intensity

Table 3 Safety record: reported are toxicities with an at least one grade 2 event (toxicity graded by CTC V2; rates in brackets)

	Grade 1	Grade 2	Grade 3	Grade 4
Hematological toxicity				
Anemia	11 (26)	2 (5)	–	–
Febrile neutropenia				1 (2)
Neutropenia	4 (9)	2 (5)	4 (9)	1 (2)
Leucopenia	3 (7)	5 (12)	2 (5)	–
Thrombocytopenia	3 (7)	–	–	–
Non-hematological toxicity				
Peripheral neuropathy	12 (28)	–	1 (2)	–
Liver	3 (7)	2 (5)	–	–
Diarrhea	3 (6)	8 (19)	7 (16)	–
Nausea/vomiting	11 (26)	10 (23)	1 (2)	–
Fatigue	3 (7)	3 (7)	1 (2)	–
Abdominal pain	1 (2)	–	1 (2)	–
Fever	1 (2)	3 (7)	–	–
Depression	–	2 (4)	–	–
Weight loss	–	2 (4)	–	–
Constipation	3 (7)	1 (2)	–	–
Anorexia	2 (5)	1 (2)	–	–

Toxicity was not recorded for four patients. Rates are calculated among 43 patients

Responses and survival

All enrolled patients were analyzed for time to progression and survival and 45 patients were assessed for tumor response to treatment (two patients had non-measurable disease). In intent-to-treat analysis the objective response rate was **13**% (95% CI 4.8–25.7%) with one complete and five partial responses observed (Table 4). Objective response rates did not differ between patients with liver-dominant metastases ($N = 12$, RR 17%) and all others ($N = 35$, RR 11%) ($P = 0.637$) (Table 5). The median times for response duration in responders and time to progression and survival in all were 3.8, 2.7 and 9.5 months, respectively. The 1-year survival was 40% and the 2-year survival 8% (Table 6 and Fig. 1).

Table 4 Antitumor biologic activity: tumor response to therapy assessed on intent to treat basis for patients with measurable disease, $n = 45$ (two patients had non-measurable disease)

Response	*n*	%	95% CI
Complete response[a]	1	2	0.1–11.3
Partial response[a]	5	11	3.6–23.1
Stable disease[b]	12	27	13.9–40.4
Progressive disease	20	44	28.3–57.8
Treatment discontinuation prior to evaluation	7	16	6.2–28.3

CI confidence interval

[a] Refers to confirmed objective responses

[b] Refers to an at least 4 months duration of disease stabilization

Table 5 Antitumor biologic activity in patients with predominately liver involved ($n = 12$) versus all others ($n = 35$)

	Liver predominately ($n = 12$)	Other ($n = 35$)
CR	–	1 (3)
PR	2 (17)	3 (9)
SD	3 (25)	9 (26)
PD	6 (50)	14 (40)
Treatment discontinuation prior to evaluation	1 (8)	6 (17)
NE	–	2 (6)

Objective response rates (CR and PR) did not differ between the two groups (17% for liver only versus for all other 11%, $P = 0.637$)

Discussion

It is recommended that therapeutic management of patients diagnosed with metastatic carcinoma of unknown primary site be guided by recognition of the well defined clinicopathologic CUP subsets to which each case fits in [23]. Unfortunately the majority of patients diagnosed with CUP fall into the large poor prognosis group, with liver, bone or multiple organ involvement. They have tumors resistant to therapy and survival figures even for patients treated at reference centers remain at a disappointing 6 months median life span post-diagnosis [4]. A grimmer prognosis is reflected in cancer registries with median duration of survival of only 2–3 months in unselected CUP populations [24,25]. It is therefore a reasonable recommendation that patients with poor prognosis CUP should either receive a low-toxicity chemotherapy or be treated in a clinical trial if they fulfill the entry requirements and such an option is locally available [23,26].

The therapeutic effects achieved by the irinotecan–oxaliplatin combination in this multicenter phase-II trial are summarized as a 13% response rate, minimum 4 months' disease stabilization in 27% of treated patients and 40% of patients being alive at 1 year. This response rate assessed by intent-to-treat analysis runs at the low edge of previously reported tumor response rates of other regimens investigated during the last 10 years in the same clinical setting, in patients with poor prognosis CUP. However, in most of these trials the response rates are below 20% when an intent-to-treat analysis is used (Table 7) [27–32]. Moreover it must be noted that the median survival of patients treated in this trial was 9.5 months, which ranks high among this set of trials and the toxicity relatively low, which is also of major importance when considering palliative therapy. The IROX regimen was well tolerated, with 16% of patients experiencing grade-3 diarrhea. Other toxicities were practically absent. Haematological toxicity was an exception, nausea and vomiting was mild and transient peripheral neuropathy occurred in one only case. With the agents in the IROX regimen expected to provide reasonable cover for lung, colorectal, gastric and ovarian/peritoneal primary cancers, it is debatable why this regimen did not produce a higher objective response rate. We regard such questions to refer to the concept that CUP tumors, although heterogeneous in origin, model a distinct clinical entity with specific genetic/phenotypic profile [33].

When considering the whole group of CUP, excluding established favorable subsets [mainly women with adenocarcinoma involving only axillary lymph nodes or the peritoneal cavity and patients with poorly differentiated carcinoma consistent with a germ cell tumor or neuroendocrine carcinomas], phase-II trials with platinum ± taxane combinations have produced response rates up to 40% [3]. However, the antitumor effect recorded in most studies has been invariably of short duration and even with highest response rates, it failed to extend median survival above a roof level of 10–12 months' duration [34].

Our data and previous experience indicate that novel treatment approaches beyond empirical chemotherapy need to be explored in poor prognosis CUP. Investigations on biologic therapeutics, which are in line with translational

Table 6 Time-to-event endpoints (median follow-up: 53.9 months)

Parameter	Median time (months)	95% CI
Survival (all patients)	9.5	5.5–13.6
Time to progression (all patients)	2.7	2.1–3.3
Response duration (CR and PR pts)	3.8	1.8–5.8

CI confidence interval

Table 7 Selection of phase-II trials in patients with poor prognosis CUP

Regimen	Most frequent involved site/sites	*n*	ORR	OS	Grade 4 hem tox (%)	Non-hem tox grades 3–4 (%)	Publication year	Ref.
Epirubicin–cisplatin-continous infusion 5FU	Multiple-liver	43	19	5.7	21	21	2000	[27]
Paclitaxel-5FU or carboplatin–etoposide (random)	Liver-bone	34	17.5	6.5	24	47	2001	[28]
Carboplatin–gemcitabine–paclitaxel	Multiple	120	25	9	46	40	2002	[29]
Carboplatin–gemcitabine–paclitaxel[a]	Liver dominant metastases[a]	51	15					[29]
Alternating dose-dense doxorubicin–cyclophosphamide and etoposide–cisplatin	Liver–bone	82	38	10	54	19.5	2002	[30]
Carboplatin–gemcitabine	Multiple-liver	50	28	7.8	38	10	2006	[31]
Weekly paclitaxel–carboplatin	Multiple-liver	42	16.5	8.5	2	25	2007	[32]
Irinotecan–oxaliplatin	Multiple-liver	47	13	9.5	2	24	Present study	

ORR objective response rates (analyzed on an intent-to-treat basis)

[a] Subgroup analysis of the above study

research data [35] have already been started and initial results as second-line treatment show promises for treatment improvement [36]. It is believed that optimal combinations of biologics with cytotoxics deserve careful consideration in this clinical setting. Ongoing molecular research and focused translational studies are critical in advancing a more thorough understanding of the biology of these tumors and improving the management of patients with such tumors [37]. Moreover, the introduction of biological targeted therapeutics in the treatment of metastatic common cancers raises ethical issues when considering treatment of patients diagnosed with metastatic cancer from an occult primary because they miss the option of a targeted therapy, which would be indicated should a primary be identified [38,39].

In summary, the combination of irinotecan and oxaliplatin was well tolerated and yielded a modest antitumor activity, which was comparable to other regimens in patients with poor-prognosis CUP, particularly when we consider the achieved survival and favorable profile of toxicity. Although this regimen may be seen as an additional therapeutic option in the arsenal against cancer of unknown primary it also indicates that novel therapeutic approaches must be tested. It is now the time to pursue large, and possibly international, phase-III trials to assess the clinical value of therapies that incorporate biologic targeted and cytotoxic therapeutics compared with conventional chemotherapy.

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