Irinotecan plus carboplatin for patients with carcinoma of unknown primary site

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Carcinoma of unknown primary site (CUP) is rarely encountered in clinical practice and optimal chemotherapy has not yet been established. This phase II study was conducted to evaluate the efficacy and toxicity of combined irinotecan + carboplatin therapy in chemotherapy-naive patients with CUP. Irinotecan was administered at 60 mg m⁻² as a 90-min intravenous infusion on days 1, 8 and 15. Carboplatin was administered at an area-under-the curve of 5 mg ml⁻¹ min as a 60-min intravenous infusion on day 1. This cycle was repeated every 28 days for up to six cycles. Forty-five patients were enrolled in the study. An intent-to-treat analysis revealed an objective response rate to the treatment of 41.9% (95% confidence interval, 27.0–57.9%). The median time to progression was 4.8 months and the median survival was 12.2 months. The 1- and 2-year survival rates were 44 and 27%, respectively. The most frequent grade 3 or more severe adverse events were leukopaenia (21%), neutropaenia (33%), anaemia (25%) and thrombocytopenia (20%). Thus, the combination of irinotecan plus carboplatin was found to be active in patients with CUP. Therefore, the regimen may be one of the potentially available chemotherapeutic options for community standard of care in patients with a good performance status.

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Carcinoma of unknown primary site (CUP) represents a group of heterogeneous malignancies that is diagnosed based on the presence of a metastatic disease without an identifiable primary tumour at the time of presentation. Carcinoma of unknown primary site accounts for approximately 3–5% of all newly diagnosed patients with malignancies (Briasoulis et al, 2008b).

The prognosis of CUP is generally poor, with a median overall survival time (OS) of approximately 6–12 months. Some of these patients with favourable and unique clinical and/or pathologic features may show prolonged survival with specific treatment approaches (Pavlidis et al, 2003). However, most of the patients fit into the category of poor prognosis. Many investigators have made efforts to develop optimal chemotherapeutic regimens based on the empiric approach, and platinum-based combination chemotherapy is considered to be one of the suitable treatment options for a large proportion of these patients (Pavlidis et al, 2003).

Irinotecan is a potent inhibitor of DNA topoisomerase I. It exhibits excellent antitumour activity, not only against a broad spectrum of tumours in experimental models (Kano et al, 1992; Misawa et al, 1995). Carboplatin is an analogue of cisplatin, with less severe non-haematological toxicities (Briasoulis et al, 2000; Yonemori et al, 2005). No cross-resistance has been found between irinotecan and carboplatin, and a synergistic effect of irinotecan with carboplatin has been shown in in vitro studies (Kano et al, 1993).

In an earlier study conducted by us, although the combination of docetaxel plus cisplatin produced favourable results in patients with CUP, treatment discontinuation sometimes became necessary because of the renal toxicity induced by cisplatin (Mukai et al, 2003; Yakushiji et al, 2006). Carboplatin has proven to be as effective as cisplatin against chemo-sensitive CUP, with an additional advantage of being better tolerated and more convenient in clinical practice (Briasoulis et al, 2000). In this study, we report the results of a phase II trial conducted to evaluate the effect of irinotecan plus carboplatin in the treatment for CUP.

PATIENTS AND METHODS

Patients

Patients who had histologically confirmed metastatic carcinoma were eligible for enrollment in this study, if the following evaluations did not reveal a primary site: complete history, physical examination, blood counts and blood chemistry examinations, including serum α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG) as tumour markers in both sexes, carbohydrate antigen 125 (CA125) as a tumour marker in women, prostate-specific antigen (PSA) as a tumour marker in men, urinalysis, head and neck examination with pharyngeal
Treatment

Irinotecan was administered at the dose of 60 mg m⁻² dissolved in 100 ml saline as a 90-min intravenous infusion, followed by carboplatin at an area-under-the-curve of 5 mg min⁻¹ m⁻² dissolved in 250 ml of saline or 5% dextrose as a 60-min intravenous infusion. Irinotecan administration was planned for days 1, 8 and 15 of each cycle, and that of carboplatin was planned for day 1 of infusion. Irinotecan administration was planned for days 1, 8 and 15 if the leukocyte count was ≥3000 per µl or the neutrophil count was ≥1500 per µl, platelet count ≥100 000 per µl, serum total bilirubin ≤1.5 mg dl⁻¹, serum alanine aminotransferase ≤2 times the upper limit of normal, serum creatinine ≤1.5 mg dl⁻¹). Patients with active infection, bowel obstruction, interstitial pneumonitis, uncontrolled severe heart disease, uncontrolled diabetes mellitus, pregnant or lactating women, symptomatic brain metastasis, severe coexistent medical illness or a past history of hypersensitivity to drugs were excluded from the study. Patients who had massive pleural effusion or ascites that required drainage or active concomitant malignancy were also excluded. Patient subgroups that were suitable for well-established treatments (i.e., men with blastic bone metastases showing features of adenocarcinoma and elevated PSA, women with axillary lymph nodes as the only site of disease showing features of adenocarcinoma, woman with papillary serous carcinoma of the peritoneum, patients with either cervical or inguinal lymph node involvement only with features ofsquamous cell carcinoma, patients with poorly differentiated carcinomas suggestive of germ cell tumour with elevated levels of AFP and/or β-HCG, patients with low-grade, well-differentiated neuroendocrine carcinoma and patients with carcinoma involving a single, potentially resectable site) were also excluded from the study. The protocol was approved by the institutional review board. All patients provided written informed consent before their enrollment.

Irinotecan was administered on day 1 if the leukocyte count was ≥3000 per µl or the neutrophil count was ≥1500 per µl, the platelet count was ≥75 000 per µl, serum total bilirubin was ≤1.5 mg dl⁻¹, serum alanine aminotransferase was ≤2 times the upper limit of normal, the serum creatinine was ≤1.5 mg dl⁻¹ and any non-haematological toxicities, with the exception of alopecia, were ≤grade 1. The dose on day 8 and/or day 15 was omitted entirely if the counts or toxicities did not satisfy the above criteria.

Dose modification of carboplatin from AUC 4 to AUC 5 was allowed if febrile neutropaenia or grade 4 thrombocytopaenia was observed, or if platelet transfusion was required.

Response and toxicity evaluation

All patients were re-evaluated for response after completion of two cycles of treatment, and the response categories were assigned based on the RECIST criteria (Therasse et al., 2000). Repeat scans at 8-week intervals were performed to confirm the response. The final response category assigned to these patients represented the best response obtained during the treatment course. Toxicities were evaluated according to the National Cancer Institute's Common Toxicity Criteria, Version 2.0, after every cycle and at the end of the study treatment.

Statistical analysis

The primary end point of this study was the objective response rate, defined as the proportion of patients with complete response or partial response in the intent-to-treat (ITT) population, in turn, defined as patients who had received at least one cycle of irinotecan and carboplatin. The secondary end points included safety and tolerability, time to tumour progression (TTP), OS, and the 1- and 2-year survival rates.

The sample size was determined using Simon’s Minimax two-stage design for phase II studies. The response rates to chemotherapy of patients with CUP have been reported as approximately in the range of 20–40% (Briasoulis et al., 2000; Greco et al., 2000a, b; Dowell et al., 2001), so that the null hypothesis was that the true response rate was less than or equal to 30% (not considered to be clinically meaningful). The alternative hypothesis was that the true response rate was more than or equal to 50%. A total of 39 patients were required as the target sample to ensure results with 80% power and a type I error rate of 5%, for rejecting the null hypothesis that the true response probability was less than or equal to 30%. The enrollment of 45 patients was planned to fulfill the requirement of 39 patients, because some patients might need to be potentially excluded from the analysis because of failure to receive at least one cycle of irinotecan and carboplatin.

The objective response rate was reported as a percentage, along with the 95% confidence interval. The TTP and OS were determined by the Kaplan–Meier method. All the statistical analyses were performed using SPSS 12.0J (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Between May 2003 and November 2007, 45 patients were enrolled in this clinical trial. The patient characteristics are listed in Table 1. The median age was 59 years (range, 36–78 years), and the median performance status (PS) was 1 (range, 0–2). The median number of disease sites per patient was two (range, 1–7).

Twenty-three patients had lymph node involvement only. Serum tumour markers were assessed at the baseline pretreatment evaluation in 43 patients. The median number of tumour markers showing elevated serum levels was 5 (range, 0–10). Eighty-seven percent (N=39) of the patients showed elevated serum levels of tumour markers at the time of diagnosis (Table 2).
Clinical Studies

Table 1  Patient characteristics

| Characteristics       | No. of patients |
|-----------------------|-----------------|
| No. of patients enrolled | 45              |
| Age (years)           |                 |
| Median                | 59              |
| Range                 | 36–78           |
| Sex                   |                 |
| Male                  | 23              |
| Female                | 22              |
| ECGD performance status |               |
| 0                     | 19              |
| 1                     | 22              |
| 2                     | 4               |
| Histologic type       |                 |
| Adenocarcinoma (well and moderately differentiated) | 21 |
| Poorly differentiated adenocarcinoma | 9  |
| Squamous cell carcinoma | 7           |
| Poorly differentiated carcinoma | 5 |
| Clear cell carcinoma  | 1               |
| Small cell carcinoma  | 1               |
| Undifferentiated carcinoma | 1 |
| No. of disease sites  |                 |
| 1                     | 13              |
| 2                     | 10              |
| ≥3                    | 22              |
| Site of disease       |                 |
| Lymph node            | 40              |
| Lung                  | 6               |
| Bone                  | 4               |
| Liver                 | 8               |
| Adrenal               | 2               |
| Malignant effusion    | 4               |
| Soft tissue           | 3               |
| Other                 | 6               |
| Prognostic index      |                 |
| Cuine et al (2002)a   |                 |
| Good risk             | 29              |
| Poor risk             | 16              |
| van der Gaast et al (1996)b |       |
| Good risk             | 19              |
| Intermediate risk     | 19              |
| Poor risk             | 7               |

ECGD = Eastern Cooperative Oncology Group. aGood-risk patients had a performance status of 0 or 1 and normal serum lactate dehydrogenase (LDH) levels; poor-risk patients had a performance status of ≥2 or elevated serum LDH levels. bGood-risk patients had a performance status of 0 and serum alkaline phosphatase (ALP) levels of <1.25 × normal range (N); intermediate-risk patients had a performance status of ≥1 or serum ALP levels of ≥1.25 × N; poor-risk patients had a performance status of ≥1 and serum ALP levels of ≥1.25 × N.

Efficacy

Forty-five patients were enrolled in this study. All the enrolled patients were included in the analysis for TTP and OS, and 43 patients who had received at least one cycle of irinotecan plus carboplatin were assessed for tumour response to treatment. Two patients who were withdrawn from the study because of the appearance of toxicity in cycle 1 were considered as not evaluable. Objective response was observed in 18 patients, including complete response in two and partial response in 16 patients. Stable disease was observed in 10 patients and progressive disease in 15 patients. The results of an ITT analysis revealed an objective response rate of 41.9% (95% confidence interval, 27.0–57.9%); the response rate was 41.3% in the 30 patients with well-to-poorly differentiated adenocarcinoma and 50.0% in the 23 patients with lymph node involvement only. The median TTP was 4.8 months, and the median OS was 12.2 months. The 1- and 2-year survival rates were 44 and 27%, respectively (Figure 1).

Toxicity

The toxicity data are listed in Table 3. Bone marrow suppression (leukopaenia, neutropaenia and thrombocytopenia) and gastrointestinal toxicities, such as nausea, vomiting, diarrhoea and appetite loss, were the most frequent. There were no treatment-related deaths in this study.

Overall, 180 treatment cycles were administered and the median number of cycles per patient was five (range, 1–6). Of the 180 cycles, in 9.4% (17 episodes), the day-8 administration of irinotecan was withheld because of neutropaenia (11.8%), anaemia (5.9%), thrombocytopenia (35.3%) or non-haematological toxicity (41.1%), including two episodes of fatigue, three episodes of nausea, two episodes of infection and one episode of palpitation. Furthermore, in 27.2% of the cycles, the day-15 administration of irinotecan was withheld because of neutropaenia (14.3%), thrombocytopenia (65.3%), non-haematological toxicity (16.3%), including one episode of appetite loss, one episode of nausea, two episodes of diarrhoea, four episodes of febrile neutropaenia and patient refusal for personal reasons (two instances). The day-8 or day-15 irinotecan was withheld at least once in 24 (53%) patients. Five patients (11.1%) with anaemia required red blood cell transfusion and four patients (8.9%) with thrombocytopenia required platelet transfusion. Dose modification of carboplatin was necessary in 15.5% of the patients (seven patients).

DISCUSSION

Recently published trials, in the literature, of regimens containing platinum agents for CUP have reported objective response rates in the range of 13–53% and median OS in the range of 6.0–16.2
months (Table 4). In two of these trials conducted to evaluate the activity of first-line platinum-based combination chemotherapy, the treatment regimen included irinotecan (Culine et al, 2003; Briasoulis et al, 2008a). According to one, the combination of irinotecan plus cisplatin yielded an objective response rate of 38% and median OS of 6 months (Culine et al, 2003). In another study limited to poor-prognosis patients, irinotecan plus oxaliplatin yielded an objective response rate of 13% and median survival time of 9.5 months, with 40% of the patients still alive at 1 year (Briasoulis et al, 2008a). The patient background, especially the prognostic characteristics, may have an influence on the treatment outcome. Two-thirds of the patients in this study were prognostically good-risk patients, with a low percentage of patients having liver metastasis and a large percentage of patients with the disease extent being limited to the lymph nodes; in contrast, in most of the recently published series, the majority of the patients were prognostically poor-risk patients and/or had liver metastasis. Therefore, potential bias would make a reliable comparison of the results of the present and previous studies difficult.

Interestingly, the Kaplan–Meier analysis in this study revealed a 2-year survival rate of 27%, with some patients even showing long-term survival (Figure 1). The results of chemotherapy in a total of 1515 patients enrolled in 45 trials including 10 patients or more revealed an objective response rate of 38% and median survival of 6 months (Culine et al, 2003). In another study limited to poor-prognosis patients, irinotecan plus oxaliplatin yielded an objective response rate of 13% and median survival time of 9.5 months, with 40% of the patients still alive at 1 year (Briasoulis et al, 2008a). The patient background, especially the prognostic characteristics, may have an influence on the treatment outcome. Two-thirds of the patients in this study were prognostically good-risk patients, with a low percentage of patients having liver metastasis and a large percentage of patients with the disease extent being limited to the lymph nodes; in contrast, in most of the recently published series, the majority of the patients were prognostically poor-risk patients and/or had liver metastasis. Therefore, potential bias would make a reliable comparison of the results of the present and previous studies difficult.

In addition, the advances in the development of many molecular-targeted agents provide opportunities to explore various new combination therapies containing both cytotoxic and molecular-targeted agents for patients with CUP. Several studies have demonstrated the immunohistochemical expression of relevant molecular targets at high frequencies in tissue specimens (Massard et al, 2007). A phase II trial of bevacizumab plus erlotinib revealed substantial activity of this combination in patients treated previously or patients who had not received treatment because of the presence of poor-prognostic features (Hainsworth et al, 2007). In a preliminary study, treatment with paclitaxel plus carboplatin used in combination with bevacizumab plus erlotinib yielded an objective response rate of 48% (N = 19 out of 40) and was well tolerated as first-line chemotherapy for patients with CUP (Greco et al, 2008). After first-line platinum-based combination chemotherapy, the approach of empiric second-line chemotherapy has shown little promise, with extremely low response rates (Hainsworth et al, 2001, 2005). Therefore, tailor-made first-line chemotherapy by genomic typing or addition of molecular-targeted drugs may be important in the treatment of CUP, which includes heterogeneous cancers, rather than the development of second-line chemotherapy.

In this study, the most frequently encountered toxicity was haematological toxicity and some patients needed blood transfusion or dose reduction of carboplatin. The dose delivery was fairly smooth in the chemotherapy-naive patients with CUP as compared with that in our earlier phase I study of combined irinotecan plus carboplatin in patients with heavily treated ovarian cancer (Yonemori et al, 2005). Among the advantages of this regimen are

![Figure 1](https://example.com/figure1.png)

**Figure 1** Kaplan–Meier analysis to determine the time to progression (dotted line) and overall survival (solid line).

| Profile                  | Frequency (%) | No. of grade 3 (%) | No. of grade 4 (%) |
|--------------------------|---------------|--------------------|--------------------|
| Haematologic toxicity    |               |                    |                    |
| Leukopaenia              | 75.6          | 6 (13.3)           | 4 (8)              |
| Neutropaenia             | 80            | 6 (13.3)           | 9 (20)             |
| Anaemia                  | 93.3          | 8 (17.8)           | 3 (6.7)            |
| Thrombocytopaenia        | 68.9          | 7 (15.6)           | 2 (4.4)            |
| Non-haematologic toxicity|               |                    |                    |
| Fatigue                  | 60            | 0 (0)              | 0 (0)              |
| Appetite loss            | 46.7          | 0 (0)              | 0 (0)              |
| Nausea                   | 82.2          | 1 (2.2)            | 0 (0)              |
| Vomiting                 | 26.7          | 1 (2.2)            | 0 (0)              |
| Diarrhoea                | 57.8          | 4 (8)              | 0 (0)              |
| Constipation             | 42.2          | 0 (0)              | 0 (0)              |
| Skin rash                | 20            | 0 (0)              | 0 (0)              |
| Febrile neutropaenia     | 13.3          | 5 (11.1)           | 1 (2.2)            |

| Table 3 | Toxicity profiles (frequency > 10%) |
|---------|------------------------------------|
that it is easy to adjust the irinotecan dose during each chemotherapy cycle according to the individual toxicity profiles and to manage the chemotherapy on an outpatient basis without prophylactic use of granulocyte-stimulating factor or erythropoietin.

In conclusion, combined irinotecan plus carboplatin chemotherapy appears to exert satisfactory activity and to be reasonably well tolerated in patients with CUP. Many conventional chemotherapies have been reported as the community standard of care for patients with CUP. This regimen was moderately well tolerated and may become established as one of the treatment options in patients with a good PS.

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Conflict of interest

Katsumata N: Honoraria (Sanofi-aventis, Pfizer, Nippon Kayaku, Kyowa Hakko Kogyo, Zeneca). His family members have no financial interest or conflict of interest in relation to this study. None of the authors or their immediate family members have any financial interest or conflict of interest in relation to this study.

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|| Group | Reference | Regimen | N | RR | MST (m) | 1 year | 2 year |
|---|---|---|---|---|---|---|---|
| Doublet | Briasoulis et al (2000) | Carbo–P | 77 | 38.7% | 13.0 | NA | NA |
| | Voog et al (2000) | Cis–P | 42 | 32% | 8.0 | NA | NA |
| | Greco et al (2000a) | Cis–D | 26 | 26% | 8.0 | 40% | 28% |
| | Dowell et al (2001) | Carbo–E | 17 | 19% | 8.3 | 26% | NA |
| | Saghatanian et al (2001) | Cis–E→Cis–E–B–I | 30 | 40% | 9.4 | NA | 28% |
| | Cis–F | 18 | 44% | 16.1 | NA | 39% |
| | Culine et al (2002b) | Dx–Cy→Cis–E | 82 | 39% | 10.0 | NA | NA |
| | Culine et al (2003) | Cis–G | 39 | 55% | 8.0 | NA | NA |
| | Park et al (2004) | Cis–P | 37 | 42% | 11.0 | 38% | 11% |
| | El-Rayes et al (2005) | Carbo–P | 22 | 23% | 6.5 | 27% | NA |
| | Pittman et al (2006) | Carbo–G | 51 | 30.5% | 7.8 | 26% | 12% |
| | Briasoulis et al (2008a) | Ox–Ir | 47 | 13% | 9.5 | 40% | NA |
| | Pentheroudakis et al (2008) | Carbo–D | 47 | 32% | 16.2 | NA | NA |
| | This study | Carbo–Ir | 45 | 41.9% | 12.2 | 44% | 27% |
| Triplet or more | Pannis et al (2000) | Cis–F–Ep | 43 | 23% | 5.8 | NA | NA |
| | Greco et al (2000b) | Carb–P–E | 71 | 48% | 11.0 | 48% | 20% |
| | Guardiola et al (2001) | Cis–Dx–Cy | 22 | 50% | 10.7 | NA | NA |
| | Macdonald et al (2002) | Cis–F–Mit | 31 | 27% | 7.7 | 28% | 10% |
| | Greco et al (2002) | Carbo–G–P | 113 | 25% | 9.0 | 42% | 23% |
| | Balan˜a et al (2003) | Cis–G–E | 30 | 36.6% | 7.2 | 26% | NA |
| | Piga et al (2004) | Carbo–Dx–E | 102 | 26.5% | 9.0 | 35.2% | 18.1% |
| | Greco et al (2004) | Carbo–P–E→G–Ir | 111 | 33% | 9.1 | 35% | 16% |
| | Palmeni et al (2006) | Cis–G–P | 33 | 48.5% | 9.6 | NA | NA |
| | Schneider et al (2007) | Cis–G–V | 33 | 42.3% | 13.6 | NA | NA |
| | Greco et al (2008) | Carb–G–Cape | 33 | 39% | 13.7 | 35.6% | 14.2% |

B = bleomycin; Bv = bevacizumab; Cape = capcetabin; Carbo = carboplatin; Cis = cisplatin; Cy = cyclophosphamide; D = docetaxel; Dx = doxorubicin; E = etoposide; Ep = epirubicin; Er = erlotinib; F = 5-FU; G = gemcitabine; If = ifosfamide; Ir = irinotecan; m = months; Mit = mitomycin C; MST = median survival time; NA = not available; Ox = oxaliplatin; P = paclitaxel; RR = response rate; V = vinorelbine. *1 year = 1 year survival rate. **2 year = 2 year survival rate.
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