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Review

Cisplatin alone or combined with gemcitabine in carcinomas of unknown primary: Results of the randomised GEFCAPI 02 trial

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KEYWORDS
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Abstract *Purpose:* To compare the overall survival rates of good-prognosis carcinomas of an unknown primary site (CUPS) patients treated with cisplatin alone (C) or in combination with gemcitabine (CG).

Patients and methods: Good prognosis was defined according to the GEFCAPI (Groupe d'Etude Français des Carcinomes de site Primitif Inconnu) classification by PS (Performance Status) $\leqslant 1$ and LDH (Lactate Deshydrogenase) within the normal range. Patients were randomly assigned to receive C or CG. Patients in the C arm received cisplatin 100 mg/m^2 repeated every 3 weeks. In the CG arm, chemotherapy consisted of gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 100 mg/m^2 IV on day 1, repeated every 3 weeks. The original plan was to accrue 192 patients in order to detect a 20% difference in overall survival.

Results: Fifty-two patients were enrolled (arm A: 25; arm B: 27). The trial was stopped early due to insufficient accrual. The median overall survival (OS) rate was 11 months [95% confidence interval: 9–20] and 8 months [95% CI: 6–12], in the CG arm and in the C arm, respectively. The 1-year survival rate was 46% [95% CI: 28–64] in the combination arm and 35% [95% CI: 19–56] in the C arm (log rank test: $p = 0.73$). The median progression-free survival

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(PFS) rate was 5 [95% CI: 3–11] and 3 [95% CI: 1–8] months in the CG and in the C arm, respectively. The 1-year PFS rate was 29% [95% CI: 15–48] in the combination arm and 15% [95% CI: 5–35] in the C arm (log rank test: $p = 0.27$). No toxic deaths occurred. Grade 3–4 neutropenia (63% versus 12%) and grade 3–4 thrombocytopenia (37% versus 4%) were more frequent in the CG arm than in the C arm.

Conclusion: A non-significantly better outcome was observed with CG as compared to C in patients with CUP and a non-unfavourable prognosis. The toxicity profile of the combined arm was represented by haematologic toxicity with thrombocytopenia and leuconeutropenia. International collaboration is required to conduct phase III trials in patients with CUP.

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1. Introduction

Carcinomas of unknown primary (CUPs) remain a heterogeneous entity that share the unique clinical characteristic of metastatic disease with no identifiable origin at the time of therapy. They account for about 3–5% of all cancers.[1] The major step for the diagnosis of CUPs is recognising one of the described clinico-pathologic entities with a specific treatment and better outcome, although these entities account for only approximately 15% of CUPs.[2]

During the last decade, many studies have been conducted to better define the prognosis of patients with CUP. These studies give contradictory results and identify different prognostic factors.[3–5] Nevertheless, a few of these prognostic models have been formally validated. The French CUP Study Group (GEFCAPI) developed a simple prognostic system that allocates patients to two subgroups with a good and an unfavourable prognosis, and a median survival rate of 12 and 4 months, respectively. This model, using the performance status and the serum LDH level, was successively validated on an independent set of patients.[5] As the overall outcome of patients with CUP is poor, the benefit of chemotherapy over the best supportive care is still unclear and the optimal chemotherapy regimen remains to be determined.[6] Although no evidence-based standard therapy has been established from phase III trial data, guidelines including the Standard, Options, and Recommendations (SOR), and the "Minimal Clinical Recommendations" produced by the European Society of Clinical Oncology (ESMO) recommend the use of platin-based chemotherapy in patients with CUP (SOR/ESMO).[2,7] A previous randomised phase II trial conducted by the GEFCAPI demonstrated that the combination of cisplatin and gemcitabine yields promising antitumour activity and a favourable pattern of tolerance in patients with CUPs.[8] Based on these data, the GEFCAPI decided in 2003 to launch two parallel randomised trials in patients with CUP: GEFCAPI 03 tested the role of chemotherapy in patients with CUP and an unfavourable prognosis while GEFCAPI 02 tested cisplatin with or without gemcitabine in patients with a favourable prognosis. This article reports the results of the GEFCAPI 02 trial. Despite the selection of a homogeneous subpopulation of patients belonging to "the good prognosis' group, the overall outcome remains poor, with an expected median overall survival of 12 months.[5] Thus, this group of patients may be considered as a non-unfavourable group.

2. Patients and methods

2.1. Eligibility criteria

The GEFCAPI 02 trial was approved by the Bicêtre Board for the Protection of Persons subjected to Biomedical Research. This phase III randomised trial was conducted in 12 French cancer centres from May 2003 to June 2007. It is registered under the following number: NCT00126269. Eligibility criteria included age over 18 years, histologically confirmed CUP, no previous chemotherapy, absolute granulocyte count $\geqslant$1,500/μl, platelet count $\geqslant$100,000/μl, normal serum creatinine or creatinine clearance >60 ml/min, normal liver tests (serum bilirubin level $\leqslant$1.5-fold the upper normal limit); a predicted non-unfavourable outcome according to the GEFCAPI index: Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a normal serum LDH value. Patients with either measurable or non measurable disease were accrued.

Patients were excluded if they had any of the following features: a CUP belonging to subsets with specific treatment, i.e. women with adenocarcinoma exclusively involving the axillary lymph nodes, women with papillary serous carcinoma of the peritoneum, patients with squamous carcinoma exclusively involving cervical or inguinal lymph nodes, carcinomas with neuro-endocrine features, young males with an undifferentiated CUP of the middle line, males with bone metastases and an elevated serum prostate-specific antigen level, and patients with carcinoma at a single potentially resectable tumour site; symptomatic brain metastases; a history of a previous malignancy with the exception of skin cancer or cervical carcinoma *in situ*; pregnant or lactating women; severe coexistent medical illnesses. All patients signed a written informed consent form.

2.2. Pretreatment evaluation

Patients were required to undergo at least the following procedures : a complete medical history and physical examination, a chemistry profile including in men serum prostate-specific antigen, alpha-fetoprotein and human chorionic gonadotrophin determination, chest roentgenogram, computerised tomography scan of the thorax, abdomen and pelvis, a mammogram in women and a directed radiologic work-up of any symptomatic areas. Specific pathologic evaluation was additionally required for patients with light microscopic diagnosis of poorly differentiated carcinoma to exclude, if possible, other malignancies. Immunoperoxidase staining with antibodies directed against leukocyte common antigen, cytokeratins (CK7 and CK20), TTF1 (Thyroïd Transcription Factor-1), neuroendocrine markers (chromogranin and synaptophysin), and melanoma markers (S-100 protein and HMB-45) was recommended.

2.3. Chemotherapy and patient monitoring

Patients were randomised to receive either cisplatin 100 mg/m^2 IV on day 1 at 3-week intervals, alone (C) or combined with gemcitabine 1250 mg/m^2 IV on days 1 and 8 (CG arm). Intravenous hyperhydration and anti-emetic prophylaxis were systematically given. Routine laboratory tests including electrolytes, creatinine, total protein, albumin, calcium, glucose, alkaline phosphatase, total and direct bilirubin, AST (Aspartate transaminase), ALT (Alanine transaminase), and prothrombin time were evaluated on the first day of each course of chemotherapy. Additional complete blood cell counts were obtained weekly. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0).[9]

A complete re-assessment of all metastatic sites was scheduled every two cycles of chemotherapy. Patients were assigned a response category based on Response Evaluation Criteria in Solid Tumours (RECIST) criteria.[10] A complete response required the total disappearance of all clinical and radiological detectable diseases for at least 4 weeks. A partial response was defined as a greater than 30% reduction in the sum of the one-dimensional measurements for a minimum of 1 month, with no new lesions appearing. Progressive disease was defined as a greater than 20% increase in sum of the one-dimensional measurements or the appearance of any new lesion. The number of planned cycles was six. Responding patients or those with non-progressive lesions could receive additional courses at the discretion of the treating physician. After completion of therapy, patients were monitored at 3-month intervals until disease progression. All patients were followed up until the time of death.

The European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) was submitted to the patients before treatment and after two chemotherapy cycles. The analysis was to be performed according to EORTC recommendations.

2.4. Statistical design

The design of this study was that of a randomised phase III trial with overall survival (OS) as the primary endpoint. Assuming a median survival of 12 months in the C group, 192 patients were required to detect a difference between a 12 months OS of 50% (group C) and of 70% (group CG) with a power of 80% and a 5% level two-sided log rank test. Secondary objectives were the response rate, progression-free survival (PFS), toxicity, and quality of life (measured by the EORTC-QLQ C30 questionnaire).

Results are expressed as percentages or medians (range). Survival was calculated using the Kaplan Meier method,[11] with Rothman's 95% confidence intervals [95% CI].[12]

3. Results

3.1. Patient characteristics

Between May 2003 and June 2007, 52 patients were enrolled onto the study. Because of the low accrual rate, the trial was closed before reaching the 192 planned patients. Twenty-five were randomly assigned to the C arm. Twenty-seven were allocated to the combination CG arm. Patients were well-matched in terms of initial characteristics (Table 1). The median age of the population was 58 years (37–77). Baseline characteristics are reported in Table 1.

3.2. Treatment delivery

The median number of cycles was 4 (1–6) and 3 (1–6) in the CG arm and the C arm, respectively.

3.3. Response

Forty-four patients were evaluable for response (85%). The overall objective response rates were 19% (IC: [6%;40%]) and 16% (IC: [5%;40%]), in the CG and C, respectively. Two patients achieved a complete response in the C arm. In terms of the clinical benefit rate, defined as the overall objective response rate and stable disease rate, there was a trend in favour of the combination arm with 67% in the CG arm (18 pts) compared to 56% in the C arm (14 pts), but the difference was not statistically significant. Stable disease was observed in 13 patients (48%) in the CG arm and in 18 patients in the C arm (40%).

Table 1
Baseline characteristics.

Characteristic	CG arm ($n = 27$)	C arm ($n = 25$)
Age, years		
Median (range)	58 (37–74)	58 (44–77)
Sex n (%)		
Male	16 (59)	14 (56)
Female	11 (41)	11 (44)
ECOG performance status n (%)		
0	10 (37)	6 (24)
1	17 (63)	19 (76)
Site of disease *n* (%)		
Viscera		
Lungs	13 (48)	12 (48)
Liver	6 (22)	8 (32)
Bones	10 (37)	11 (44)
Pleura	3 (11)	2 (8)
Skin	1 (4)	2 (8)
Peritoneum	2 (7)	2 (8)
Adrenal glands	2 (7)	3 (12)
Brain	1 (4)	2 (8)
Other	6 (22)	1 (4)
Lymph nodes	13 (48)	15 (60)
Supra-clavicular	1 (4)	5 (20)
Mediastinal	8 (30)	11 (44)
Retroperitoneal	5 (20)	5 (20)
Cervical	3 (11)	6 (24)
Other	2 (8)	5 (20)
Immunochemistry		
TTF1 +/−/unknown	3 (11.5)/16 (61.5)/8 (27)	5 (20)/17 (68)/3 (12)
CK7 +/−/unknown	18 (66.5)/5 (18.5)/4 (15)	21 (84)/3 (12)/1 (4)
CK 20 +/−/unknown	4 (15)/18 (66.5)/5 (18.5)	5 (20)/18 (72)/2 (8)

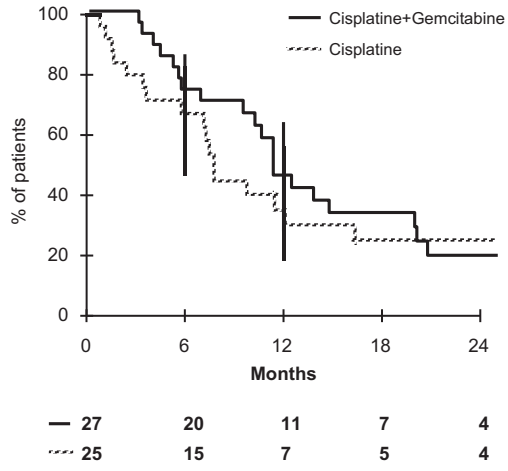

Fig. 1. Overall survival.

3.4. Survival

In september 2007 (cut-off date) the median follow-up was 38.3 [7;42] and 40.3 months [3;43] in the CG arm and the C arm, respectively. The median OS duration was 11 months [95% CI: 9;20] and 8 months [95% CI: 6;12], in the CG arm and in the C arm, respectively. The 1-year survival rate was 46% [95% CI: 28;64] in the combination arm and 35% [95% CI: 19–56] in the C arm. Median PFS was 5 months [3;11] and 3 months [1;8] in the CG arm and in the C arm, respectively. The PFS rate at 1 year reached 29% [15;48] and 15% [5;35] in the CG arm and the C arm, respectively. Overall, a non-significantly better outcome was observed for patients treated with CG compared to C, considering OS (HR = 0.9 [0.5;1.7], $p = 0.73$) (Fig. 1) and PFS (HR = 0.7 [0.4;1.3], $p = 0.27$) (Fig. 2).

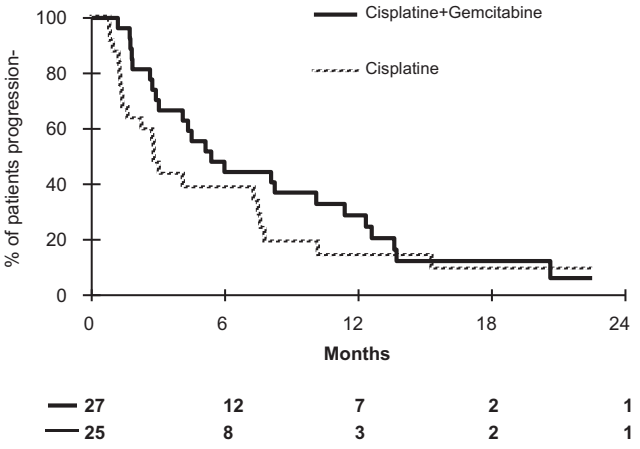

Fig. 2. Progression-free survival.

Table 2
Toxicity profile: incidence of grade 3–4 adverse events (%).

	GC arm ($n = 27$)	C arm ($n = 25$)
Haematologic toxicity		
Neutropenia	63	12
Febrile neutropenia	11	0
Thrombocytopenia	37	4
Anaemia	22	4
Non-haematologic toxicity		
Infection	0	0
Nausea- vomiting	26	25
Renal toxicity	7	0
Asthenia	19	25

3.5. Toxicity

No toxic deaths occurred. Regarding haematologic toxicities, both neutropenia and thrombocytopenia were more frequently observed in the combination arm compared to the monotherapy arm. The incidence of grade 3–4 neutropenia was 63% versus 12%, respectively. Three cases of febrile neutropenia were reported in the CG arm (11%), not statistically significant compared to the C arm (0%). The incidence of grade 3–4 thrombocytopenia was 37% versus 4%. Considering blood transfusion, 22% of the patients in the GC arm required erythrocyte transfusion compared to 8% in the C arm. Fifteen percent of the patients in the CG arm required platelet transfusions, whereas none was needed in the

C arm. A summary of adverse events is reported in Table 2.

3.6. Quality of life

In the study design, quality of life was considered as a secondary endpoint, but this analysis was not performed due to insufficient patient accrual and the low rate of answers for the second evaluation, after two cycles: only 13 out of the 27 patients in the CG arm and 10 out of 25 in the C arm.

4. Discussion

There is currently no established standard chemotherapy regimen for the treatment of patients with CUP which do not fall into the recognised specific entities. Only a few randomised trials have attempted to establish such a regimen.[13] One of the main limitations in conducting trials in patients with CUP is the heterogeneity of this cancer patient population. Major progress has been achieved through the identification and validation of simple prognostic factors that can be used either to select or to stratify patients for randomised trials.[5] The present randomised study attempted to test whether a cisplatin–gemcitabine doublet could improve the outcome of patients with a non-unfavourable prognosis according to the GEFCAPI prognostic system versus single agent cisplatin. Unfortunately, as previously reported in other studies by other groups, the trial was closed early before completing its planned enrolment due to poor accrual.[13,14] In this population of 52 patients, results report a non-significant improvement in PFS (median: 5 months versus 3 months) and OS (median: 11 months versus 8 months) in the CG arm compared to the C arm. Of note, the results reported here with the cisplatin–gemcitabine doublet are consistent with those of previous phase II trials reported by our group,[8] and by others,[15] indicating that this regimen may be regarded as a valid option in patients with CUPs and a non-unfavourable prognosis (See Table 3). The clinical benefit, defined as an overall response rate and stabilised disease was interesting in this incurable disease (66% in the CG arm and 56% in the C arm). The combination also appeared interesting given the wide range of activity, with data in numerous clinical situations, such as non-small cell lung carcinoma, bladder cancer, and ovarian cancer, pancreatic/biliary cancer. The results of the carboplatin–gemcitabine doublet have also been reported.[16] The overall response rate was 30.5% in 46 patients evaluable for efficacy, and the median overall survival duration reported was 34 weeks (7.8 months).[16] Gemcitabine was also previously combined with docetaxel in a phase II trial and yielded a response rate of 40% and a median overall survival time of 10 months [0;32] in 35 patients.[17] Finally, in a pooled data analysis of 29 phase II trials investigating 38 regimens in 1820 patients affected by CUPs, cisplatin was reported as one of the only two drugs with meaningful activity.[18] Paclitaxel was added to the gemcitabine-carboplatin doublet, followed by weekly paclitaxel for responders in 120 patients, in an attempt to improve the response rate and overall survival.[19] Unfortunately, although an overall response rate of 25% was achieved, with a median survival of 9 months, the toxicity profile, with alopecia, common grade 3–4 myelosuppression, despite the frequent use of Colony-Stimulating Factor, and common significant neuropathy may be considered unjustified, and not consistent with the last ESMO guidelines.[6,19] The difficulty of recruiting patients with CUP for clinical trials is universal. A recent example is the phase III trial attempting to assess paclitaxel, carboplatin, and etoposide versus gemcitabine–irinotecan followed by a maintenance treatment with targeted therapy, which had to stop accrual before completion after entering 198 out of 320 planned patients.[15] As the prolongation of survival is modest, the realistic aims of current treatment should be symptom palliation with preservation of quality of life. The toxicity profile of the combination arm was haematologic, with 63% of grade 3–4 neutropenia and 37% of grade 3–4 thrombocytopenia. The incidence of febrile neutropenia remains acceptable with a rate of 11%, and no toxic death reported. The high rate of haematologic events might be explained by the doses and the dose-intensity of the schedule. Both drugs were administered with higher doses than in previous association reported in urothelial carcinoma (G:1000 mg/m^2, j1, j8, j15 C:70 mg/m^2, j1, j1 = j28),[20] in biliary tract (G:1000 mg/m^2, j1,j8,j15, C:25 mg/m^2, j1, j8, j15, every 4 weeks),[21] or Non Small Cell Lung Cancer.[22] Furthermore, the toxicity reported in the GEFCAPI 01 trial, in the GC arm was less frequent with

Table 3
Results of clinical trials testing the efficacy of gemcitabine–cisplatin doublet.

	n	Mean/median age (years)	Response rate CR + PR (%)	Median overall survival (months)	Risk group; good/poor (%)
Isik M et al.[15]	23	54.9 (mean)	30.4	10	43.5 56.5
Culine et al.[8]	38	58 (med)	55	8	31 69
Gross-Goupil et al.	27	58 (med)	19	11	100

23% of grade 3–4 neutropenia and only 3% of febrile neutropenia, and 18% of grade 3–4 thrombocytopenia. To improve current results, there is obviously a need to go beyond conventional chemotherapy in patients with CUPs. However, little is known about the biology of CUPs,[23] and 'targeted' therapies have only recently been assessed.[24] Conflicting data have been reported regarding the expression of Her-2 in tissue specimens from patients diagnosed with CUP: 4% ($n = 54$) and 33% (16/45), respectively, in two different series.[25,26] High EGFR (Epidermal Growth Factor Receptor) expression was reported in a large proportion (66%) of patients with CUP in one series, with patients bearing EGFR-expressing CUPs tending to achieve better response rates with platin-based chemotherapy (50% and 22% response rates in patients with EGFR-positive and EGFR-negative tumours, respectively, $p = 0.046$).[25] A recent phase II trial included 60 patients who received carboplatin–paclitaxel for a CUP, followed in 44 patients (73%) by maintenance bevacizumab and erlotinib. Thirty-two patients (53%) achieved a response, and the median survival and the median PFS duration was 12.6 months and 8 months, respectively, which compare favourably with previous experiences with chemotherapy alone.[27]

Another potential way of improving the treatment of CUPs, would be better tissue characterisation. Promising preliminary data have been reported with molecular profiling to predict the tissue of origin in patients with CUPs.[28–30] The GEFCAPI in collaboration with the Agendia team, has reported the results of a prospective feasibility study using a diagnostic gene expression-based classifier (CupPrint^{TM}).[31] Based on these results, the GEFCAPI will soon be conducting a randomised trial comparing cisplatin–gemcitabine versus individualised therapy based on the results of molecular analyses in patients with CUPs (GEFCAPI 04). Based on previous experience, there is no doubt that international collaboration will be required to answer this important question.

Conflict of interest statement

None declared.

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