Carboplatin, doxorubicin and etoposide in the treatment of tumours of unknown primary site

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The aim of this study was to assess the activity and toxicity of a platinum-based treatment on a group of patients with unknown primary tumours (UPTs). Patients with a diagnosis of UPT underwent a standard diagnostic procedure. Treatment was started within 2 weeks from diagnosis and consisted of carboplatin 400 mg m^{-2} day 1, doxorubicin 50 mg m^{-2} day 1, etoposide 100 mg m^{-2} days 1–3, every 21 days. Response was evaluated after three courses and treatment continued in case of objective response (OR) or symptom control. A total of 102 patients were eligible. The median age was 59 years, sex male/female 54/48, histology was mainly adenocarcinoma or poorly differentiated carcinoma. Nodes, bone, liver and lung were the most frequently involved sites. In all, 79 patients received at least three courses of treatment; 26 patients received six courses or more. Six complete responses and 21 partial responses were observed, for a total of 27 of 102 ORs or 26.5% (95% confidence interval 18.2–36.1%). The median survival was 9 months and median progression-free survival was 4 months. Toxicity was moderate to severe, with 57.8% of patients experiencing grade III–IV haematological toxicity, mainly leucopenia. The regimen employed has shown activity in tumours of unknown primary site, but was associated with significant toxicity. Such toxicity may be considered unjustified, given the large proportion of patients with tumours not likely to respond. Efforts should therefore be addressed to identify predictors of response to chemotherapy, thus limiting aggressive treatment to those patients who could benefit from it.
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Unknown primary tumours (UPTs) are now recognised as an autonomous, although heterogeneous, nosographic entity, with considerable clinical relevance, as they account for 5% of all tumours. Until recently they were approached with more emphasis on diagnosis than on treatment. Much emphasis was placed on trying to ascertain the site of origin of the tumour. This approach is slowly being discarded, at least in reported series, although it widely resists in clinical practice, in particular in non-specialised centres. There are two main reasons for abandoning extensive investigation in an attempt to find the site of origin. Extensive diagnostic procedures cause discomfort for the patient, require time and cause delay of treatment. In addition, they are often fruitless (Hainsworth and Greco, 1993; Abbruzzese *et al*, 1995; Schapira and Jarrett, 1995).

For the minority of tumours that have been identified in the last two decades as being potentially sensitive to chemotherapy (van der Gaast *et al*, 1990; Pavlidis *et al*, 1992; Abbruzzese *et al*, 1995; Lenzi *et al*, 1997; Greco and Hainsworth, 2001b), the diagnostic

procedures will delay these patients from receiving effective treatment.

By restricting diagnostic procedures to a minimum, and with an early start of chemotherapy, median survival has improved from 3–6 months of the past (Altman and Cadman, 1986; Alberts *et al*, 1989) to around 1 year in recently reported series (Briasoulis *et al*, 2000; Greco *et al*, 2000a).

We have conducted a multicentre phase II trial in patients with UPT, where diagnostic procedures were limited and where treatment was started soon after presentation. Although in autopsy series the majority of patients with UPT are diagnosed with diseases poorly responsive to treatment (Nystrom *et al*, 1977), there is a substantial minority of patients with primary tumours that are sensitive to chemotherapy, such as germ cell tumours, ovarian and breast cancer. The regimen chosen for this study, a combination of carboplatin, doxorubicin and etoposide, contains drugs active against these more chemosensitive tumours, and employed at dosages potentially able to induce major responses We considered that if an improvement of response rate occurred, this might result in improved outcome for an unselected group of patients with UPTs, and that this would justify the anticipated toxicity of the regimen.

This paper describes the results with emphasis on response to treatment, toxicity and survival.

PATIENTS AND METHODS

Patients were enrolled in the study if they had a histologically confirmed diagnosis of carcinoma, adenocarcinoma or undifferentiated tumour and no evidence of the site of origin based on routine haematological and biochemical investigation, tumour markers, chest X-ray and abdominal ultrasound. This initial investigation was then completed by CT of abdomen and thorax, and bone scan. Patients with carcinoma or undifferentiated tumour in cervical nodes as the only site of disease were excluded, as they usually deserve specific diagnostic and therapeutic procedures as for head and neck tumours. Other eligibility criteria were: bidimensionally measurable disease and/or elevated tumour markers; age 70 years or less, ECOG performance status $\leqslant 2$; and adequate bone marrow (WBC $\geqslant 4000\,\mu l^{-1}$; platelets $\geqslant 100\,000\,\mu l^{-1}$), renal (creatinine and urea $\leqslant 1.5 \times N$, upper limit of normal) and liver function (bilirubin $\leqslant 1.5 \times N$; liver enzymes $< 3 \times N$). Patients were excluded if there was a previous diagnosis of cancer at known sites, coexistent cardiac failure or ischaemia, psychiatric disorder or other severe medical illness and less than 3 months of life expectancy.

Following initial workup and assessment of all measurable disease, other diagnostic procedures were those dictated by clinical presentation. The intention was to start treatment within 2 weeks from the diagnosis of UPT.

The pathology workup included immunohistochemistry and, in a limited number of cases, electron microscopy to ascertain epithelial differentiation in some lesions composed of small cells. Immunohistochemistry was carried out on specimens fixed routinely in 10% neutral-buffered formalin for 24 h. Primary antibody was incubated at 4°C for 16–18 h; avidin–biotin–peroxidase complex method was used as a immunodetection method. A variety of antibody reagents were used: cytokeratins – AE1/AE3, CAM 5.2, CK 20, CK 7; epithelial membrane antigen; vimentin; carcinoembryonic antigen; calretinin; S100 protein – placental alkaline phosphatase; thyroglobulin; prostate-specific antigen (PSA); MOC-31; estrogen receptor protein; CA-125; CA 19.9; and tumour-associated glycoprotein (B72.3). Pathology reports were reviewed and classified by one of the authors (RM); no centralised pathology review was carried out.

Patients were treated as outpatients with the following chemotherapy regimen: carboplatin 400 mg m^{-2} day 1, doxorubicin 50 mg m^{-2} day 1 and etoposide 100 mg m^{-2} days 1–3; cycles were repeated every 21 days. At subsequent cycles, if haematological parameters had not recovered by day 22, treatment was delayed for 1 week. Since this was common, most centres adopted a 28-day interval for each cycle. Reduction of doses by 25% was mandatory at the first cycle if patients had advanced age (>65), poor performance status (ECOG 2), multiple organ involvement by the disease, poor renal, cardiac or liver function. This reduction was often maintained throughout all courses based on tolerance. In patients starting with full doses of drugs, a dose reduction of 25% was also planned for subsequent administrations in case of grade 3–4 leucopenia or thrombocytopenia. The use of growth factors on an individual basis was left to the discretion of attending physicians. During therapy, blood counts were not, as a rule, monitored on a weekly basis.

Concomitant antiemetic therapy included 5-hydroxytryptamine-3 antagonists and dexamethasone.

Response was evaluated after three cycles of therapy according to the WHO criteria. Stable and responding patients were subjected to additional cycles based on clinical evaluation. Subsequent treatment in the case of tumour progression at any time was at the discretion of the attending physician.

Response was based on two-dimensional measurement of all sites of disease. Complete response (CR) was complete disappearance of tumour, partial response (PR) reduction of 50% or better of the sum of products of the diameters, stable disease (SD)

reduction lower than 50% or less than 25% increase, progressive disease (PD) increase of more than 25% or appearance of new lesions. Survival was calculated from entry in the study till the end of follow-up or death. Progression-free survival was calculated from entry in the study to progression or death from disease (or end of follow-up if not progressed). Toxicity was evaluated according to the WHO criteria (Miller *et al*, 1981).

Statistical evaluation included analysis of survival (Kaplan–Meier), comparison of survival curves (log-rank test) and χ^2 test to assess association between baseline characteristics and toxicity. Carboplatin dosages were converted for statistical purposes to AUC dosing by the Cockroft–Gault (Cockcroft and Gault, 1976) and Calvert (Calvert *et al*, 1989) formulas.

The study was started in January 1991 as a three-institutions study (Ancona, Verona, Pesaro), and was open by the end of the year to the other collaborating centres. Accrual was halted in December 1996; follow-up data were collected on 31st December 2002.

The study was approved by the Ethical Committee of University of Ancona. Written informed consent was requested from patients for entry in the study.

RESULTS

A total of 113 patients were registered in the study. Of these, 11 patients were judged not eligible: seven because of a previous diagnosis of cancer at known sites, three because they had poorly differentiated carcinoma in cervical lymph nodes as the only site of disease. In one patient, who started treatment before completion of initial workup, abnormal PSA levels led quickly to appropriate diagnostic procedures and to the discovery of the prostatic origin of the tumour. Three patients who exceeded the age limit but who were judged by their physicians to be fit to receive the proposed treatment were included in the analysis.

In all, 102 patients were evaluated; the median age was 59 years (range 25–73 years), male/female ratio of 1.12 (54/48); 51 patients had a performance status ECOG 0, 43 patients ECOG 1, eight patients ECOG 2. Histology was well-differentiated adenocarcinoma (WDA) in 38 cases, poorly differentiated carcinoma or adenocarcinoma (PDC) in 50, squamous cell carcinoma (SCC) in four and undifferentiated neoplasms (UN) in 10 cases. The majority of patients had visceral or bone involvement (60 patients or 58.8%). Eight female patients had peritoneal disease and three patients (two of which male) had disease confined to axillary nodes. Other relevant characteristics of the patients are depicted in Table 1. A total of 74 patients (72.5%) received at least three courses of treatment; 26 patients (25.5%) received six courses of treatment or more.

We observed six CR (5.9%) and 21 PR (20.6%), for a total of 27 of 102 objective responses (OR) or 26.5% (95% confidence interval (CI) 18.2–36.1%), 23 SD (22.5%) and 46 PD (45.1%) (Table 2). Response was not assessable in six patients (NA, 5.9%). These were patients who died with disease before response could be assessed, and are grouped with nonresponders (intention-to-treat analysis). At the date of last follow-up (December 2002), 94 patients had died. Two of them committed suicide, both with progressing disease.

The median survival was 9 months, with 1-year survival of 35.2%, 2-year survival of 18.1%, 5-year survival of 6.3% and median progression-free survival of 4 months (Table2 and Figure 1).

The median survival was 23 months for responders, 11 months for SD patients and 6 months for nonresponding patients (Figure 2). The median duration of response was 8 months.

Toxicity was moderate to severe (Table 3), with 58 patients experiencing grade 3–4 haematological toxicity (mainly leucopenia, but also thrombocytopenia and anaemia) and one patient

**Table 1** Characteristics of the patients (*N* = 102)

	No. of patients	%
Age (years)		
Median	59	
Range	25–73	
Sex		
Male	54	52.9
Female	48	47.1
Performance status		
ECOG 0	51	50.0
ECOG 1	43	42.2
ECOG 2	8	7.8
Histology		
WDA	38	37.3
PDC	50	49.0
SCC	4	3.9
UN	10	9.8
Extension		
Locoregional	28	27.5
Disseminated	74	72.5
Topography		
Supradiaphragmatic	30	29.4
Subdiaphragmatic	29	28.4
Both sides	43	42.2
Number of involved sites		
1	29	28.4
2	31	30.4
3	17	16.7
⩾4	25	24.5
Number of metastases		
1	13	12.7
2	6	5.9
3	12	11.8
⩾4	71	69.6
Main involved sites		
Supraclavicular nodes	28	27.5
Hylomediastinal nodes	26	25.5
Abdominal nodes	20	19.6
Bone	31	30.4
Liver	27	26.5
Lung	22	21.6
Ascites	12	11.8
Pleural effusion	10	9.8
Nodes/soft tissues only	42	41.2
Visceral/bone involvement	60	58.8
Main symptoms		
Pain	65	63.7
Gastrointestinal	30	29.4
Respiratory	20	19.6
Fever	16	15.7
Weight loss >10%	9	8.8
Laboratory parameters		
Hb <12	28	27.5
Any liver index ⩾1.25 × N	42	41.2
ALP ⩾1.25 × N	21/95	22.1
LDH ⩾1.25 × N	26/86	30.2
CEA >5	36/96	37.5
CA 19.9 >40	25/84	29.8
CA 125 >40	33/69	47.8
Any epithelial marker abnormal	62	60.8
Any germ cell marker abnormal	9	8.8

ECOG = Eastern Cooperative Oncology Group; WDA = well-differentiated adenocarcinoma; PDC = poorly differentiated carcinoma or adenocarcinoma; SCC = squa-squamous cell carcinoma; UN = undifferentiated neoplasms. ALP = alkaline phosphatase; LDH = lactate dehydrogenase; CEA = carcino embrionic antigen; CA 19.9 and CA 125 = carbohydrate antigens CA 19.9 and CA 125.

Table 2 Results of treatment (*N* = 102)

	No. of patients	%
Responses		
CR	6	5.9
PR	21	20.6
SD	23	22.5
PD	46	45.1
NA	6	5.9
Duration of response		
Median (months)	8	
Range	2–102+	
Overall survival		
Median (months)	9	
At 12 months	35.3%	
At 5 years	6.3%	
Progression-free survival		
Median (months)	4	
At 12 months	16.3%	
At 5 years	3.6%	
Grade III–IV toxicity		
Anaemia	31	30.4
Leucopenia	48	47.1
Thrombocytopenia	28	27.5
Nonhaematological toxicity	10	9.8

CR = complete response; PR = partial response; SD = stable disease; PD = progres-progressive disease; NA = not assessable.
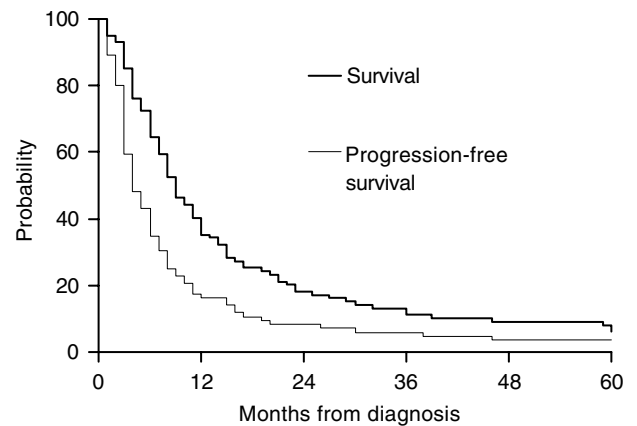
Figure 1 Kaplan–Meier estimates of survival and progression-free survival for the whole group of patients with UPT (*n* = 102).

dying from sepsis during chemotherapy-induced neutropenia. Toxicity other than haematological was limited to occasional gastrointestinal toxicity, while complete reversible alopecia was the rule. One patient had clinically important disturbance of electrolytes and another had transient ECG abnormalities. Details of doses and toxicity are listed in Table 3. Delivered dose intensity, due to either poor general conditions or toxicity, was approximately two-thirds of projected dose intensity (Table 3).

No variable was found associated with toxicity among those assessed, which included: age, sex, performance status, extension of disease, liver involvement, abnormality of liver indexes, calculated AUC for carboplatin and dosage reduction of cytotoxic drugs (Table 4).
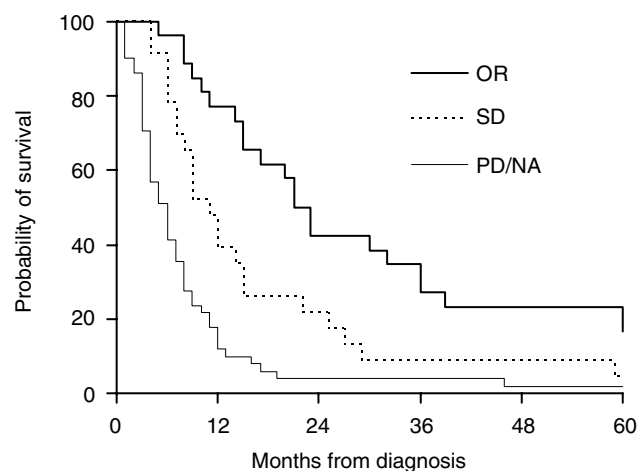
Figure 2 Kaplan–Meier estimates of survival for patients with: (A) OR, $n = 27$; (B) SD, $n = 23$; and (C) no response (PD/NA, $n = 52$). Log-rank test: a vs b, $P = 0.008$; a vs c, $P < 0.001$; b vs c, $P = 0.003$.

DISCUSSION

The current approach to management of patients with UPT consists of only limited diagnostic investigation followed by an early start of treatment.

With this approach, and with diagnostic and therapeutic improvements (Greco and Hainsworth, 2001b), prognosis seems to have improved to some extent. Response rates to chemotherapy range between 23 and 46% and median survival is between 8 and 11 months (Briasoulis et al, 1998a; Culine et al, 1999; Briasoulis et al, 2000; Greco et al, 2001a; Culine et al, 2002; Greco et al, 2002). It is difficult to compare results of different series, because of the lack of standardised clinical prognostic factors and the limitations of most of the studies, which include small number of patients, variable characterisation of clinical features and short observation period. In general, it appears that more recent chemotherapy regimens that employ platinum compounds, and often etoposide or taxanes or both (Briasoulis et al, 1998a; Briasoulis et al, 2000; Saghatchian et al, 2001; Greco et al, 2001a) are superior, in terms of response rate, to more traditional drugs (Kelsen et al, 1992; Nole et al, 1993; Falkson and Cohen, 1998; Lofts et al, 1999).

In the current report, we have treated 102 patients with UPT with an intensive combination of three drugs (carboplatin, doxorubicin and etoposide). A similar combination was used by Briasoulis et al (1998a) with lower dosage of carboplatin ($300 \, mg \, m^{-2}$) and anthracycline (epirubicin $45 \, mg \, m^{-2}$). We selected these drugs on the basis of their known efficacy in those subsets of UPT that are sensitive to chemotherapy (e.g. germ cell tumours, ovarian carcinomas). We chose to employ these drugs at dosages that might produce as great number of major responses as possible. At these doses toxicity, especially myelosuppression, was expected. The anticipation of toxicity led to restrictive inclusion criteria such as age limit, good general condition and normal organ function, with 92% of patients having ECOG PS of 0 or 1.

We obtained 26.5% of ORs and a median survival of 9 months. Survival at 1 year was 35.3 and 6.3% at 5 years. These results are similar to those of other recently published reports (Table 5), although, as previously indicated, reliable comparison cannot be made between different series.

Toxicity in our patients was moderate to severe. No factor could be identified that was associated with major toxicity. In particular, calculated AUC for carboplatin was not associated with toxicity of chemotherapy. A dose reduction of 25% was routinely applied to

Table 3 Dose intensity and toxicity, overall and by cycle

Cycle no.	No. of patients	Dose delivered % of projected				Delivered dose intensity mg m^{-2} week^{-1} (% of projected)				Grade III–IV toxicity number of patients (%)					
		CBDCA AUC median (range)	CBDCA	DOX	VP16	Mean interval days	CBDCA	DOX	VP16	Overall	Haematological	Anaemia	Leucopenia	Thrombocytopenia	Gastrointestinal
1	102	7.8 (2.8–17.2)	85.4	83.2	83.5	26.8	92.8 (69.6)	11.3 (72.0)	68.9 (68.9)	31 (30.4)	28 (27.5)	7 (6.9)	27 (26.5)	9 (8.8)	5 (4.9)
2	85	7.8 (3.0–13.6)	86.3	87.3	86.8	26.8	92.6 (69.5)	11.7 (74.5)	71.0 (71.0)	23 (27.1)	19 (22.4)	8 (9.4)	12 (14.1)	6 (7.1)	4 (4.7)
3	74	7.8 (3.8–13.6)	85.6	85.6	87.3	27.8	90.0 (67.5)	11.3 (72.0)	68.9 (68.9)	19 (25.7)	16 (21.6)	9 (12.2)	15 (20.3)	7 (9.5)	4 (5.4)
4	43	7.7 (3.8–13.6)	83.2	83.8	84.9	27.8	86.7 (65.0)	10.9 (69.4)	66.2 (66.2)	16 (37.2)	15 (34.9)	8 (18.6)	10 (23.3)	6 (14.0)	2 (4.7)
5	34	7.7 (3.8–13.6)	83.5	86.0	85.8	28.9	84.4 (63.3)	10.8 (68.8)	64.8 (64.8)	10 (29.4)	9 (26.5)	6 (17.6)	3 (8.8)	5 (14.7)	1 (2.9)
6	25	7.7 (3.8–13.6)	82.8	84.8	84.8	29.3	83.0 (62.3)	10.6 (67.5)	63.3 (63.3)	3 (12.0)	3 (12.0)	2 (8.0)	1 (4.0)	2 (8.0)	0
All	102	7.8 (2.8–17.2)	84.6	84.9	85.2	27.5	89.6 (67.2)	11.2 (71.3)	68.1 (68.1)	64 (62.7)	58 (56.9)	31 (30.4)	48 (47.1)	28 (27.5)	7 (6.9)

CBDCA = carboplatin; CDDP = cisplatin; CYT = cytoxan; DOX = doxorubicin; VP16 = etoposide; AUC = area under the curve.

Clinical

Table 4 Factors examined for the effect on toxicity

Variable	Proportion of patients with grade III–IV toxicity	*P*-value
Age ≤58/>58 years	25/50 (50.0%)/33/52 (63.5%)	0.17
Gender male/female	30/54 (55.6%)/28/48 (58.3%)	0.78
ECOG 0/1–2	29/51 (56.9%)/29/51 (56.9%)	1.00
Locoregional/disseminated disease	14/28 (50.0%)/44/74 (59.5%)	0.39
Disease on one side/both sides of diaphragm	31/59 (52.5%)/27/43 (62.8%)	0.30
One–two metastatic sites/three or more	33/60 (55.0%)/25/42 (59.5%)	0.21
Up to three metastases/four or more	19/31 (61.3%)/39/71 (54.9%)	0.55
No liver involvement/liver involved	46/75 (61.3%) / 12/27 (44.4%)	0.13
No visceral involvement/visceral involvement	26/42 (61.9%)/32/60 (53.3%)	0.39
Normal LDH/abnormal LDH	34/60 (56.7%)/15/26 (57.7%)	0.78
Normal ALP/abnormal ALP	46/74 (62.2%)/9/21 (42.9%)	0.11
Normal liver indexes/abnormal liver indexes	32/59 (54.24%)/25/42 (59.52%)	0.45
No epithelial tumour markers/any marker positive	23/40 (57.5%)/35/62 (56.5%)	0.92
No drug dose reduction/doses reduced	39/70 (55.7%)/19/32 (59.4%)	0.73
CBDCA≤AUC 8/CBDCA>AUC 8	33/58 (56.9%)/25/44 (56.8%)	0.99
CBDCA≤AUC 9/CBDCA>AUC 9	39/71 (54.9%)/19/32 (61.3%)	0.55

Note: χ^2 test; *P*-values are reported. ECOG = Eastern Cooperative Oncology Group; AUC = area under the curve.

Table 5 Results of recent phase II studies in UPT with platinum-based combinations

Author	Publication year	No. of patients	Chemotherapy	Follow-up (months)	Overall response rate* (%)	Median survival (months)	1-year survival (%)
Becouarn *et al*	1989	85	CDDP/DOX/5FU/HMM	36 (max)	21.2	7	25
Rigg *et al*	1997	30	CBDCA/5FU/FA	2.8–16.6	26.7	7.8	NA
Falkson and Cohen	1998	40	CDDP/EPI/MIT	NA	50.0	9.4	NA
Briasoulis *et al*	1998a	62	CBDCA/EPI/VP16	40 (max)	37	10	NA
Warner *et al*	1998	33	CBDCA/VP16 os	0.5–33	18.2	5.6	NA
Lofts *et al*	1999	44	CDDP/5FU/TAM	NA	22.7	4	0
Greco *et al*	2000b	71	CBDCA/PTX/VP16 os	34-50	45.1	11	48
Briasoulis *et al*	2000	75	CBDCA/PTX/G-CSF	28 (median)	38.7	13	NA
Greco *et al*	2000a	26	DTX/CDDP	33 (max)	23.1	8	42
		47	DTX/CBDCA	24 (max)	19.1	8	29
Parnis *et al*	2000	43	CDDP/EPI/5FU	24–72	18.6	5.3	NA
Voog *et al*	2000	25	CDDP/VP16	NA	32	8	NA
Dowell *et al*	2001	34	PTX/FA/5FU or CBDCA/VP16	NA	17.6	6.4	26
Saghatchian *et al*	2001	30	CDDP/VP16/IFO/BLM	32 (median)	40	9.4	NA
		18	CDDP/5FU/IFN		44	16	NA
Guardiola *et al*	2001	22	CDDP/DOX/CYT	NA	45.5	10.7	NA
Macdonald *et al*	2002	31	MIT/CDDP/5FU	7–53	27	7.7	28
Culine *et al*	2002	82	CTX/DOX+CDDP/VP16	NA	29.3	10	NA
Greco *et al*	2002	120	CBDCA/PTX/GEM	8–27	23.3	9	42
Present series	2003	102	CBDCA/DOX/VP16	61–120	26.5	9	35.3

Note: NA = not available; * = by intent-to-treat analysis. BLM = bleomycin; CBDCA = carboplatin; CDDP = cisplatin; CYT = cytoxan; DOX = doxorubicin; DTX = docetaxel; EPI = epidoxorubicin; 5FU = 5-fluorouracil; FA = folinic acid; GEM = gemcitabine; HMM = hexamethyl-melamine; IFN = alfa-interferon; IFO = ifosfamide; MIT = mitomycin C; PTX = paclitaxel; TAM = tamoxifen; VP16 = etoposide; UPT = unknown primary tumours.

patients with advanced age, poor performance status, disseminated disease and poor organ function. This reduction was recommended at first course, but was often maintained through all courses of chemotherapy. It is to be noticed that all patients except two had normal renal function at study entry.

Compared to published series, the regimen we used, employed in an unselected population of patients with UPTs, resulted in no appreciable advantage in terms of response and survival. Toxicity was moderate if compared with the toxicity associated with regimens currently employed in the treatment of chemosensitive tumours; on the other hand, it exceeded the toxicity of regimens employed in tumours where chemotherapy is expected to induce a limited number of responses.

In our view, using an aggressive approach on unselected patients with UPT is not supported by our data and should not be recommended as a routine procedure. Attention should be paid, instead, to the identification of subsets of patients who may benefit from this approach.

Many efforts are now being made in the direction of molecular testing of tumour samples, both as an aid to diagnosis and as an adjunct to available clinical variables that can be used to select groups of patients well defined with regard to prognosis and sensitivity to chemotherapy (Bar-Eli *et al*, 1993; Motzer *et al*, 1995; Pavlidis *et al*, 1995; Briasoulis *et al*, 1998b; Califano *et al*, 1999; Hainsworth *et al*, 2000).

Newer imaging techniques (Tilanus-Linthorst *et al*, 1997; Kole *et al*, 1998; Lenzi *et al*, 1998; Schorn *et al*, 1999; Stevens *et al*, 1999),

such as breast MRI, positron emission tomography and other nuclear medicine techniques, that can give clues as to the site of the primary, presently remain of limited help.

There are important psychological aspects of the management of this condition. Two of our patients committed suicide. The failure to identify the site of origin adds to the anxiety and uncertainty of the condition and its treatment. The need for psychological support for these patients is considerable and requires expertise and training in the medical teams.

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Appendix

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