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Original Paper

Unknown Primary Carcinoma: Randomised Studies are Needed to Identify Optimal Treatments and Their Benefits

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This is a retrospective review of 101 patients with unknown primary carcinoma (UPC) treated between 1989 and 1994, on whom data were collected prospectively. 92 patients received platinum-based chemotherapy and 9 had single agent 5-fluorouracil (5-FU). In the platinum group, an objective response rate of 37.2% was seen, with a median duration of 4.5 months (range 1.9–17.5). There were no responses with 5-FU alone, while median survival was 6.4 months and was not different from the platinum group ($P = 0.09$). Considerable symptomatic resolution was noted, although the contribution of chemotherapy alone to this is difficult to define. The impact of tumour response on quality of life and survival in UPC requires further elucidation in prospective studies with a 'best supportive care' arm. The superiority of platinum-based treatments reported in selected subgroups cannot be applied to the whole spectrum of UPC.

Key words: unknown primary carcinoma, management review

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INTRODUCTION

PATIENTS WITH metastatic carcinoma from an unidentified primary site present oncologists with a distinct and significant problem, despite advances in tumour imaging, histochemistry, and the identification of biochemical tumour markers. They still account for 5–10% of all cancer diagnoses, and while prognosis is generally poor, there are reports of durable responses being achieved in selected subgroups with platinum-based therapy [1]. Outside these subgroups, the optimal chemotherapy regime in unknown primary carcinoma (UPC) remains to be identified, and the benefits of chemotherapy over current best supportive care are still unclear. In this series, we discuss the characteristics and treatment results of 101 cases, and focus on some important issues in the management of this condition.

PATIENTS AND METHODS

101 patients aged over 18 years with unknown primary carcinoma were treated at the Royal Marsden NHS Trust Gastrointestinal Unit between 1989 and 1994. Pretreatment evaluation consisted of a history and full clinical examination, laboratory investigations (blood count, biochemistry and urinalysis), chest radiograph, computerised tomography (CT) of the abdomen and pelvis, and tumour marker screen including the beta subunit of human chorionic gonadotrophin (HCG), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), prostate specific antigen (PSA), CA 19-9 and CA-125. Further investigations, such as upper and lower GI studies, bronchoscopy and mammography, were only performed if symptoms or signs suggested the possibility of a primary in a particular site.

Biopsy specimens were mostly obtained by excision or needle biopsy. In a few cases, fine needle aspiration cytology was sufficient to establish the diagnosis of metastatic carcinoma. In cases where sampling had been performed at a referring centre, embedded material was requested for review. Standard light microscopy criteria were used to grade cases as well, moderate or poorly differentiated adenocarcinoma and undifferentiated carcinoma. Immunohistochemical stains additionally performed included mucin staining, epithelial markers such as epithelial membrane antigen (EMA) and CAM (low molecular weight kera-

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Table 1. Treatment according to histological diagnosis

Regimen	Number of patients		
	Adenocarcinoma	Undifferentiated carcinoma	Total
*PVI 5-FU	4	0	4
Bolus 5-FU + LV (LF)	2	2	4
PVI 5-FU + interferon (IF)	1	0	1
PVI 5-FU + cisplatin/carboplatin (CF)	6	3	9
Bolus 5-FU + LV + carboplatin/cisplatin (LCF)	28	7	35
PVI 5-FU + interferon + cisplatin (ICF)	25	2	27
PVI 5-FU + epirubicin + cisplatin (ECF)	7	2	9
Etoposide + platinum ± bleomycin (BEP/EP)	3	9	12
Total	76	25	101

* PVI, protracted venous infusion; 5-FU, 5-fluorouracil; LV, leucovorin.

tin); oncofetal antigens including CEA, HCG and AFP, and PSA. Specific stains were used to identify certain tumour types. Thus, sections staining positive with Grimelius silver reaction, chromogranin, and neurone-specific enolase (NSE), in the presence of recognised morphological criteria, and accompanied by associated clinical features such as raised urinary 5-HIAA excretion, were classed as neuroendocrine tumours. Other histochemical stains used included: melanoma associated protein S100, and the haematopoietic antigens LCA (leucocyte common antigen) and CD45 which are associated with lymphomas. Patients who were initially referred as UPC and in whom a primary tumour or any of the above specific malignancies were identified, after baseline investigations, are not included in this review.

Treatment

Only 2 patients had received chemotherapy prior to referral to our unit. A list of chemotherapy regimens used in our unit is given in Table 1. 92 patients received platinum-based treatment, the other 9 received single agent 5-FU as a protracted venous infusion, or bolus injection with leucovorin (LV) or interferon biomodulation.

The combination of epirubicin, cisplatin and 5-FU (ECF) was developed in this centre to treat locally advanced gastric cancer where it has achieved response rates in phase II studies of 71% (12% CR) and median survival of 8.2 months [2].

9 cases of undifferentiated carcinoma (UC) and 3 of poorly differentiated adenocarcinoma (PDA) were treated with BEP or EP following reports of favourable outcome with this combination in these subgroups of UPC [1].

Patients were given two courses of treatment and then assessed for response according to WHO criteria [3], using repeated radiological tumour measurements and serum marker levels. Those who responded or showed disease stabilisation received further treatments (up to six or eight courses), followed by observation. Patients who showed no benefit stopped chemotherapy and continued supportive care.

Data collection and statistics

All data were collected prospectively. At each visit, prior to seeing a physician, patients were interviewed by a clinical nurse specialist using a standard questionnaire in which symptoms and toxicity were graded according to CTC criteria. This information was entered into the unit's database. The majority of these patients were treated before formal assessments of quality of life were introduced and such data were, therefore, not available.

Prognostic factors were evaluated by univariate analysis. Categorical data were compared using the chi-squared test with Fisher's exact test used where expected frequencies were less than five. Event-free and overall survival were calculated from first treatment date to the date of disease progression or death, respectively. Survival was calculated using the product-limit method of Kaplan–Meier [4], and differences in survival were examined using the log-rank test.

RESULTS

Clinical characteristics

Table 2 summarises the clinical characteristics of these 101 patients. Age (< 50 years versus > 50 years), sex and performance status (PS) did not predict for survival although PS approached statistical significance ($P = 0.06$).

Serum HCG and AFP were measured in the majority of patients and were mostly in the normal range. Among other tumour markers, CA-125 was the most commonly elevated (80% of tests).

The possibility of unrecognised ovarian cancer in female patients was considered, and we, therefore, studied patterns of CA-125 elevation as predictors of response to platinum-based treatment. 51 female patients had a baseline estimation of CA-125 performed, 46 of whom received platinum-based treatment. CA-125 was elevated in 37 out of these 46 cases (80%). Females with an elevated CA-125 level, irrespective of other simultaneously elevated markers, did not experience a longer event-free or overall survival after platinum-based treatment, when compared with similarly treated females with normal levels.

We also analysed CA-125 elevations taking into account simultaneous elevations of CEA. Rather than using absolute values, we calculated the ratio of CA-125 level to the value at the upper limit of normal for our laboratory (< 35 μg/ml), and the same for CEA elevation (normal = < 5 μg/l). Dividing the CA-125 ratio by the CEA ratio, we obtained a CA-125/CEA ratio which we attempted to correlate with survival after platinum treatment. We found that females with an arbitrarily chosen CA-125/CEA ratio of 5 or greater ($n = 8$), did not demonstrate higher response rates or improved survival after platinum-based treatment, when compared with females with a ratio of less than 5. Out of the 8 females with a ratio $\geqslant 5$, 4 had peritoneal disease, but even in this small subgroup, which closely resembles

Table 2. Clinical characteristics

Characteristics		Number of patients
Median age (years)		54
Range (years)		19–74
Sex		
Male		46
Female		55
Performance status		
WHO 0, 1		59
WHO 2, 3		42
Tumour markers		
AFP ($n = 73$)	Normal	56
	Elevated	17 (23%)
HCG ($n = 73$)	Normal	62
	Elevated	11 (15%)
CEA ($n = 73$)	Normal	33
	Elevated	40 (55%)
CA-125 ($n = 70$)	Normal	14
	Elevated	56 (80%)
CA 19-9 ($n = 50$)	Normal	24
	Elevated	26 (52%)
Number of metastatic sites ($n = 101$)		
1		39
2		34
3		16
>3		12
Dominant metastatic site ($n = 101$)		
Liver		43
Peritoneum and omentum		19
Lymph nodes		17
Lung		5
Pleura		2
Bone		1
Multiple sites (no dominant site)		14

advanced ovarian malignancy, the response rate/survival was no better than that of females with ratios of <5.

Of all patients, 61% had 2 or more metastatic sites at presentation. Patients with multiple liver or bone lesions or those with diffuse involvement of one organ were classified as having one metastatic site. The number of metastatic sites at presentation was not a significant prognostic factor ($P = 0.43$ for 1 site versus >1). A dominant metastatic site was determined based on tumour size as measured radiologically. The majority of patients had predominantly visceral disease, the commonest sites being liver (43 cases), and peritoneum or omentum (19 cases), followed by lymph nodes (17 cases). The site of main metastasis did not predict for survival when patients with predominant hepatic or lymphatic disease were compared with the rest. There were no cases of squamous cell carcinoma, or females with axillary lymphadenopathy as the predominant or only disease site. There were 10 females with peritoneal disease as the main site, and 9 males with predominantly midline or lymphatic disease, none of the latter having elevated levels of serum HCG or AFP.

Pathology

The sources of histological material are shown in Table 3, with needle biopsy of liver metastases accounting for almost half the cases. Evaluation of histopathological specimens by light microscopy revealed 76 cases of adenocarcinoma; 9 well differentiated (WDA), 29 moderately (MDA), and 33 poorly differentiated (PDA). Of the adenocarcinomas, 5 cases were of indeterminate grade. The other 25 cases fell into the category of undifferentiated carcinoma (UC). 38 specimens had histochemical staining for mucin of which 26 were positive (26 of 28 adenocarcinomas stained). In addition, a number of immunohistochemical stains were performed to confirm the diagnosis of metastatic carcinoma, to exclude primary prostatic and germ cell tumours, and also identify neuroendocrine tumours. Those most commonly employed were: EMA (positive 16 of 23), CEA (positive 9 of 11), CAM (positive 19 of 19), PSA (positive 0 of 9), HCG (positive 1 of 4) and AFP (positive 0 of 7). In none of these cases did these stains lead to identification of a primary tumour.

Treatment results

93 patients were evaluable for response. Of the 8 that were not, 4 had insufficient follow-up because of death within 1–3 weeks from start of treatment, or being lost to follow-up; 2 had non-measurable peritoneal disease, 1 stopped treatment before response could be assessed because of Hickman line blockage; and the last case had no measurable disease after surgery. These 8 cases were included in calculating the actuarial survival curves. The median duration of follow-up was 9.7 months (range 1.4–41).

95 of 101 patients received at least 2 cycles of treatment, while 55 patients completed a course of at least 6 (or 4 in the case of BEP chemotherapy). 92 patients had platinum-based treatment, 86 of which were evaluable. 3 achieved a complete response (CR, 3.5%) and 29 a partial response

Table 3. Site of tissue analysed

Site	Number of patients			
	Excision biopsy or laparotomy	Needle biopsy or endoscopy	Cytology	Total per site
Liver	1	45	1	47
Omentum/peritoneum	15	3	2	20
Lymph nodes	12	—	—	12
Lung/pleura/mediastinum	—	5	5	10
Abdominal mass	4	—	—	4
Bowel	2	—	—	2
Ovary	2	—	—	2
Bone/bone marrow	—	2	—	2
Skin	2	—	—	2
Total				101

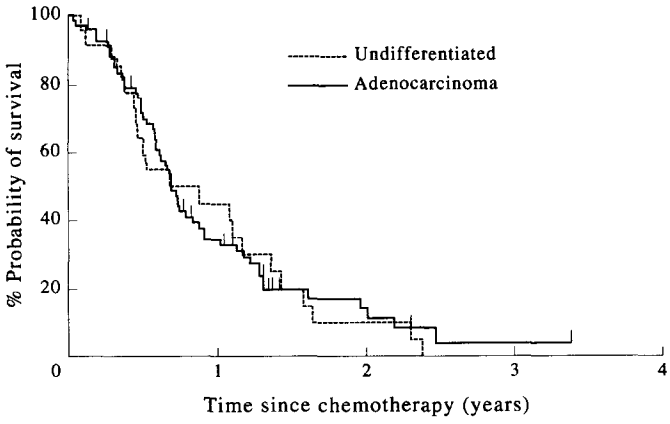

Figure 1. Comparison of survival between adenocarcinoma and undifferentiated carcinoma in patients treated with platinum-based treatments.

(PR, 33.7%), giving an objective response rate (ORR) of 37.2% (CI = 27–47.4). Median duration of response was 4.5 months (range 1.9–17.5). 69 of 76 cases of adenocarcinoma received platinum-based chemotherapy, as did 23 of 25 cases of undifferentiated carcinoma (UC). 13 out of 22 (59%) evaluable undifferentiated carcinomas responded, compared with 19 of 64 (30%) evaluable cases of adenocarcinoma ($P = 0.014$), but there was no difference in survival between these histological subtypes (Figure 1). Of the 54 platinum-treated patients who did not achieve a response, 31 had disease stabilisation, for a median duration of 3.3 months (range 1–21.3), with 3 remaining stable at 1 year, but none at 2 years. Median duration of survival for platinum-treated patients was 8.4 months, with 30 alive at 1 year, 7 at 2 years, and only 1 at 3 years.

12 patients received the combination of BEP or EP which has been reported to give superior response rates and survival in patients with PDA or UC [1]. Of these, 7 were males aged 19–63 years with either lymph node involvement or elevation of serum HCG, while the rest were females aged 42–66 years with either elevated CA-125, or peritoneal and visceral disease, or both. The response rate in these 12 patients was 58.3% (versus 30.9%, $P = 0.062$ in all other patients). Median duration of survival was 6.1 months for BEP/EP compared with 8.3 months in the rest of the series ($P > 0.1$).

Of 9 patients who received single agent 5-FU (7 adenocarcinomas and 2 UC), there were no responses but 7 patients had disease stabilisation for a median duration of 5.6 months. The median duration of survival in this group was 6.4 months with 1 patient surviving longer than 1 year. The clinical features of 11 patients who survived 18 months or longer are shown in Table 4.

Table 5 shows the site by site response rates for all cases of adenocarcinoma versus undifferentiated carcinoma. Lymphatic disease showed a significantly higher response rate in undifferentiated carcinoma compared with adenocarcinoma ($P = 0.0008$). In the whole series, a higher response rate was seen with lymphatic disease compared with liver ($P = 0.002$), and lung ($P = 0.05$), but not peritoneum and omentum ($P = 0.12$).

Sympton relief

The commonest symptoms reported were pain, weight loss and anorexia (67, 57 and 49 patients, respectively) and these were relieved in 63, 86 and 80% of cases, respectively. As quality of life assessments were not routinely made in these patients, it is not possible to assess the overall impact of sympton relief versus treatment toxicity. Additionally, all patients received full supportive care and, therefore, the contribution of chemotherapy alone to symptom relief cannot be defined.

Treatment-related toxicity

The incidence of toxicity in the platinum-based treatment group is shown in Table 6. It is of note that 67% of patients experienced neutropenia. Similarly, 74% of patients reported some degree of alopecia. There were 2 toxicity-related deaths in this series, both from septicaemia during treatment.

Identification of primary sites

Repeated imaging during therapy only identified three primary sites: a caecal, renal and cervical carcinoma. 9 patients had a postmortem examination which revealed 2 cholangiocarcinomas, 1 bronchial and 1 pancreatic carcinoma.

Table 4. Characteristics of 11 patients who survived beyond 18 months

Sex	Age	PS	Histology	Sites of disease	Main site of disease	Chemotherapy	Response	Duration (months)	Second line Rx	Response	Duration (months)	Survival (months)
F	46	1	MDA	2	None	LCF	PR	12	—	—	—	24 died
F	34	2	UC	2	Lung	ICF	PR	7	Carbo	SD	5	19 died
M	48	1	UC	1	Liver	BEP	SD	2	F	SD	3	19 died
F	69	1	PDA	1	Peritoneum	ICF	PR	2	LCF	PD	—	19 died
F	67	2	PDA	1	Peritoneum	LCF	NE	—	—	—	—	27 A
F	58	0	MDA	1	Lymphatic	LCF	CR	10	CF	PR	6	26 died
M	66	1	MDA	1	Lymphatic	ECF	CR	11	ECF	SD	4	24 died
M	61	0	UC	1	Liver	CF	SD	14	MF	SD	9	28 died
F	61	0	UC	4	Lymphatic	CF	PR	17	LCF	PR	16	28 died
M	41	1	PDA	2	Lung	ICF	SD	20	Phase 1	SD	7	29 died
M	65	2	WDA	4	Liver	ICF	PR	41*	—	—	—	41 A

PS, performance status; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; F, 5-FU; C, cisplatin/carboplatin; I, interferon; L, leucovorin; E, epirubicin (etoposide in BEP); M, mitomycin; B, bleomycin; A, still alive at cut-off date; Rx, treatment. * Ongoing response at cut-off date.

Table 5. Site by site response rates in adenocarcinoma versus undifferentiated carcinoma

	Response				
	Adenocarcinoma		Undifferentiated carcinoma		Significance
Disease	Number of cases	%	Number of cases	%	(*P* value)
Liver	9/42	21	5/15	33	0.36
Peritoneum	5/13	38	2/3	67	0.80
Lymph nodes	11/28	39	11/11	100	0.0008
Lung	6/21	29	3/7	43	0.48
Omentum	3/10	30	0/1	0	0.73
Bone	1/9	11	0/2	0	0.83

DISCUSSION

Unknown primary carcinoma is a heterogeneous tumour type, the natural history of which may differ from that of primary carcinoma. It has been suggested that clonal dominance by cells with genetic mutations favouring metastasis may occur earlier in the natural history of unknown primary tumours. The primary tumour itself may either have a slow growth rate or possible involute and, therefore, rarely manifest itself [5]. Progress in the use of diagnostic tools such as immunohistochemistry and molecular biology has led to increasing identification of primary carcinomas and non-carcinomatous tumours such as lymphomas and germ cell tumours. However, it has generally been shown that exhaustive investigation of asymptomatic systems is unwarranted, and leads to very few additional primary tumours being identified at the cost of considerable patient discomfort and expense, and with no influence on outcome [6]. Serum HCG, AFP and PSA may occasionally help to identify germ cell and prostatic primaries, but other serum markers have, in general, not been helpful in identifying primary sites, or predicting for response or survival [7]. In this series, CA-125 elevation, either as absolute serum levels, or high ratios of CA-125 to CEA elevation, had no correlation with response or survival after platinum-based treatment. However, patient numbers were small and this hypothesis requires further testing in larger prospective studies. Women with peritoneal UPC have been shown to respond favourably to platinum-based treatment (45% ORR) in 1 retrospective study of 18 patients [8]. In our series, 3 of 7 female patients with peritoneal adenocarcinoma responded (43%). There was no correlation between CA-125 elevation and response in this small group. Therefore, the usefulness of serum tumour markers in UPC is mainly to help monitor response and possibly early detection of relapse.

Several workers have attempted to identify subgroups of UPC patients with improved prognosis such as neuroendocrine tumours [9] and women with peritoneal carcinomatosis [8]. Hainsworth and associates [1] identified patients with poorly differentiated adenocarcinoma and undifferentiated carcinoma as having a markedly superior response and survival profile following platinum-based treatment. However, selection bias inherent in such subgroup analysis may confound the issue of favourable histological subtypes. Thus, in the series described by Hainsworth and colleagues, the median age of their 220 patients was 39 years with a 3:1 male preponderance, over 85% of these had a PS of 0 or 1, and 48% had mediastinal, retroperitoneal or peripheral lymph nodes as their site of bulkiest disease with only 5% having liver as their main metastatic site. Not surprisingly, 4 germ cell tumours and 6 lymphomas were diagnosed during follow-up, while the majority of long-term disease-free survivors (20 of 36 cases disease-free at a median follow-up of 61 months), were males under 50 years with predominantly lymphatic or midline disease who responded to PVB (platinum + vinblastine + bleomycin) or BEP. In our series, the 12 patients who received BEP/EP showed a trend towards a higher response rate, but no survival advantage when compared with the rest of the group.

Other large series, such as the review of 657 patients by Abbruzzese and coworkers [10], failed to show a survival advantage for chemotherapy versus no treatment and for platinum-based versus other treatments. Here, the authors proposed that the longer survival in the undifferentiated carcinoma group was inherent in the biology of this subtype, and was not affected by treatment. In our series, we failed to identify any useful prognostic factors, although there was a trend for better PS to be associated with improved outcome. Secondly, a histological diagnosis of UC was associated with a higher response rate to platinum-based therapy, in agreement with previous reports [1], but this had no impact on survival. Our analysis did not take into consideration the multiplicity of drug regimes

Table 6. Percentage treatment-related toxicity in platinum-treated patients (CTC grading)

Toxicity	% Incidence ($n = 81$)	Grade 1–2 (%)	Grade 3–4 (%)
Nausea and vomiting	65	60	5
Alopecia	74	32*	42†
Peripheral neuropathy	17	17	—
Neutropenia	67	21	46
Infection	30	23	7
Diarrhoea	41	37	4
Stomatitis	31	28	3
Plantar = palmar syndrome	19	16	3

* Grade 1, i.e. temporary hair loss; † grades 2–3, i.e. permanent hair loss.

used, although 92 patients did, in fact, have platinum-based treatment (combined with 5-FU in 80 of these). This heterogeneity of treatment schedules reflects the change in practices over the period covered in this review, but also illustrates the lack of consensus on optimal treatments, not helped by the paucity of evidence from randomised studies.

Among the arguments in favour of incorporating 5-FU in the treatment of UPC is its activity in gastrointestinal (GI) tumours coupled with reports in which a GI primary was ultimately identified in up to 53% of cases presenting with UPC [11]. Series using non-platinum-containing combinations have generally consisted of small numbers and given considerably variable results. Thus, FAM (5-FU, doxorubicin, mitomycin) gave response rates of 21 to 30% [12], while CAF (cyclophosphamide, doxorubicin, 5-FU) fared no better than single agent 5-FU with no responses in either arm, while producing more toxicity in a prospective study of 51 patients [13]. Pasterz and coworkers [14] claimed to show superiority of a platinum-based regime (FACP) over FAM, with a 26% ORR in adenocarcimoma but the response rate for FAM in this study was only 14%. Similarly, while Hainsworth and colleagues [1] retrospectively reported a 62% ORR following PVB/BEP, Milliken and coworkers [15], in a prospective randomised study of 101 patients, found no difference in ORR between PVB (32%) and doxorubicin with mitomycin-C (42%), while median survival was also similar and short (25 and 18 weeks, respectively). Lenzi and colleagues [16] reported a 32% ORR to LPF (leucovorin (LV), cisplatin, 5-FU) in a phase II study. Across the whole spectrum of UPC, Sporn and Greenberg [17] concluded that there is no favoured regime at present and that platinum-containing regimes were probably no better than non-platinum ones. They recommended FAM as a first-line combination, but whether this or indeed any other combination, is superior to modulated or PVI 5-FU, both of which have given superior results over unmodulated bolus 5-FU in metastatic colorectal cancer [18, 19], remains to be determined in prospective studies. Similarly, there are no prospective studies with a 'best supportive care' arm, and hence the question of whether chemotherapy is superior to supportive care also remains unanswered.

The response rate to platinum-based treatment of 37% reported in our series is similar to previously reported figures, and the main benefit of this often short response may be symptom relief. For the time being, there is evidence from retrospective studies that a minority of patients with UPC who fit into defined subgroups may benefit from platinum-based treatment. The greater majority of UPC patients who do not fit into these groups should be entered into randomised prospective studies with quality of life assessments, including studies where chemotherapy is compared with current best supportive care. It is hoped that such randomised studies would clarify the palliative benefit of chemotherapy in this condition, as well as rationalising the use of various chemotherapeutic agents in its management.

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