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Chemotherapy for patients with two favourable subsets of unknown primary carcinoma: Active, but how effective?

GEORGE PENTHEROUDAKIS[1], EVANGELOS BRIASOULIS[1], VASSILIS KARAVASSILIS[1], GEORGE FOUNTZILAS[2], NIKOLAOS XEROS[3], GEORGE SAMELIS[4], EPAMINONDAS SAMANTAS[5] & NICHOLAS PAVLIDIS[1]

[1]*Ioannina University Hospital, Ioannina,* [2]*Papageorgiou Hospital, Thessaloniki,* [3]*Evangelismos General Hospital, Athens,* [4]*Ippokrateion General Hospital, Athens, and* [5]*Agioi Anargyroi Hospital, Athens, Greece*

Abstract
Carcinoma of unknown primary (CUP) is characterized by dismal patient survival. The outcome of patients with two favourable risk CUP subsets was studied. Eighty patients diagnosed with either midline lymph node metastases (n = 33) or peritoneal carcinomatosis (n = 47) were analysed retrospectively. The majority had poorly differentiated adenocarcinoma or undifferentiated carcinoma, treated with platinum-taxane based chemotherapy from 1996 till 2002. Females with peritoneal carcinomatosis also underwent surgical debulking. Objective tumour regression was present in 44% of patients (nodal group 30% versus peritoneal group 53%, p = 0.066). Complete responses were seen more often in peritoneal carcinomatosis patients (nodal group 9%, peritoneal group 36%, p = 0.008). At a median follow up of 60 months, median progression-free and overall survival were 5 and 10 months respectively in the nodal group, 7 and 15 months in the peritoneal group. Five-year survival was 7% (nodal group 0% vs. peritoneal group 10%, p = 0.05). Complete responders fared better than non-CR patients. Fewer than four metastatic sites, elevated CA 125, and normal CA 19-9 levels were favourable prognostic factors for survival. Modern combination chemotherapy has satisfactory activity, with a minority of CUP patients enjoying long-term responses. Research efforts towards complete remission consolidation and molecular profiling are imperative.

Introduction

Cancer of unknown primary (CUP) accounts for 3–5% of all diagnosed malignancies and constitutes a heterogeneous group of metastatic tumour patients [1,2]. CUP has emerged as a distinct entity in which no primary tumour can be identified after thorough medical history, careful clinical assessment, and appropriate diagnostic workup. Clinicopathological subsets of patients who seem to respond more often to systemic chemotherapy, and thus fare better, have been recognized [3]. Patients with predominantly midline nodal disease as well as females with peritoneal carcinomatosis belong to such groups with relative chemosensitivity and occasional long-term survival [4,5]. We present prognostic, management, and long-term outcome data for two favourable CUP subset patients so as to investigate the impact of therapy on survival and detect characteristics defining outcome.

Material and methods

Case records of patients treated for cancer between 1996 and 2002 in five Hellenic Cooperative Oncology Group (HECOG) cancer centres were reviewed: Ioannina University Hospital, Ioannina, AHEPA University Hospital, Thessaloniki, Evangelismos General Hospital, Athens, Ippokrateion General Hospital, Athens, and Agioi Anargyroi General Hospital, Athens. Patients included in this retrospective analysis belonged to either the nodal or peritoneal favourable CUP subsets, which were defined as follows: Nodal group patients had disease consisting of retroperitoneal and/or mediastinal nodal metastases with a histological definition of

Correspondence: N. Pavlidis, Department of Medical Oncology, Ioannina University Hospital, Panepistimiou Avenue, 45110 Ioannina, Greece, Tel/fax: +30-26510-99394. E-mail: npavlid@cc.uoi.gr

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carcinoma. Pulmonary metastases may also have been present along with predominantly nodal disease burden. Peritoneal group female patients had predominantly peritoneal malignant deposits of papillary serous adenocarcinomatous or undifferentiated carcinomatous histology. A prerequisite for assigning a CUP diagnosis was failure to identify a primary tumour after careful medical history, physical examination including pelvic and rectal assessment, routine full blood count and biochemistry including serum AFP, HCG, urinalysis, stool occult blood testing, and CT of the chest/abdomen/pelvis. Appropriate endoscopic studies of the aerodigestive tract according to existing signs, symptoms, or laboratory abnormalities were performed in 55 patients (30 in the peritoneal carcinomatosis group and 25 in the midline nodal group). All women with peritoneal carcinomatosis underwent bilateral mammography and vaginal ultrasound. Histological confirmation of diagnosis of malignancy with standard light microscopic examination of haematoxylin-eosin stained tissue sections as well as appropriate immunohistochemical studies were also necessary.

Age at diagnosis, sex, metastatic sites, histological features, serum tumour markers, treatment administered, response to treatment and duration, progression-free and overall survival data were extracted from case records. The National Cancer Institute response criteria were used, with survival times being calculated from diagnosis to event or last follow-up visit. Response rates were compared by means of Fisher's exact test, while univariate and multivariate analyses were performed by means of the Cox regressional hazards model. A backward selection procedure identified the subclass of significant variables. The significant factors were kept in the model if the maximum likelihood ratio criterion had a p-value below 0.05. Exact confidence intervals (CI) were used to determine the 95% upper and lower confidence limits of response rates. The SPSS 8.0 software was used for all statistical analyses.

Results

A total of 80 patients with favourable risk CUP were identified, 47 in the peritoneal group and 33 in the nodal group. Most were aged above 60 and slightly or moderately symptomatic. Peritoneal group patients were females, with males being more numerous in the nodal group. Most tumours were poorly differentiated or undifferentiated carcinomas. Chemotherapy was the hallmark of treatment for nodal group patients, while female patients with peritoneal carcinomatosis underwent initial or interval surgical debulking. Most patients in both groups received an adequate number of cycles (median 6) of platinum-based chemotherapy, quite often combined with a taxane. The majority of them had elevated serum tumour markers during the disease course (CA125, CA 15-3, CA 19-9, CEA). Patient characteristics are given in Table I.

Roughly half of all patients responded to systemic therapy with either complete or partial tumour regression. Responses were seen more commonly in the peritoneal patient group (53% vs. 30% for the nodal group, $p = 0.066$). Of note, 17 complete responses were recorded in patients with peritoneal carcinomatosis, in contrast with only three in patients with nodal metastases ($p = 0.008$). Responses occurred in the nodal group with identical frequency in men and women. Median duration of response was nine months with disease progression eventually

Table I. Selected patient characteristics.

n	80	
Age		
Median	62	
Range	27–83	
	n	%
Sex		
Men	21	26
Women	59	74
Performance status		
0–1	54	68
2–3	25	31
Unknown	1	1
Grade (all carcinomas)		
1	7	9
2	12	15
3	55	69
Unknown	6	7
Group		
Peritoneal	47	49
Nodal	33	41
Chemotherapy administered		
Neither platinum nor taxane	6	7.5
Platinum without taxane	20	25
Taxane-based	6	7.5
Both platinum and taxane	48	60
Number of cycles delivered		
Median	6	
Range1–18		
Number of metastatic sites		
1–3	30	37.5
>3	44	55
Unknown	6	7.5
Abnormal serum tumour markers		
CA 125	34	42.5
CA 15-3	14	17.5
CA 19-9	17	21
CEA	16	20

occurring in the majority of patients. Response data are summarized in Table II.

No difference of clinical or statistical significance was detected in median progression-free survival of the two subsets at a median follow-up of 60 months (peritoneal group 7 months, nodal group 5 months). There was a trend for superior overall survival in patients with peritoneal carcinomatosis (15 vs. 10 months, $p = 0.0528$). One-fifth of patients were alive 2 years after diagnosis, though a trend for superior long-term survival in peritoneal group patients (2-year overall survival 7% for the nodal group vs. 29% for the peritoneal group) was evident. Five-year survival was 10% in the peritoneal group vs. 0% in the nodal group, in which only one long-term survivor was seen, eventually dying 38 months after diagnosis. Patients who achieved a complete response on chemotherapy relapsed later and survived longer than those who did not (median overall survival 35 vs. 10 months, $p < 0.0001$, Figure 1). Survival data are given in Table III.

Univariate and multivariate analysis for prognostic significance identified number of metastatic sites (1–3 as opposed to four or more), abnormal serum CA 125, and normal CA 19-9 levels as highly predictive factors for a superior outcome. Complete response status was not included in the prognostic factor analysis, although its achievement predicted superior outcome. On the contrary, patient management with platinum-based regimens, sex, performance status, histological grade, and peritoneal or nodal disease group did not have prognostic significance. A trend for statistical significance for female sex and peritoneal disease might have turned out to be meaningful had analysis been conducted in a larger population sample. Results of prognostic factor analyses can be seen in Tables IV and V.

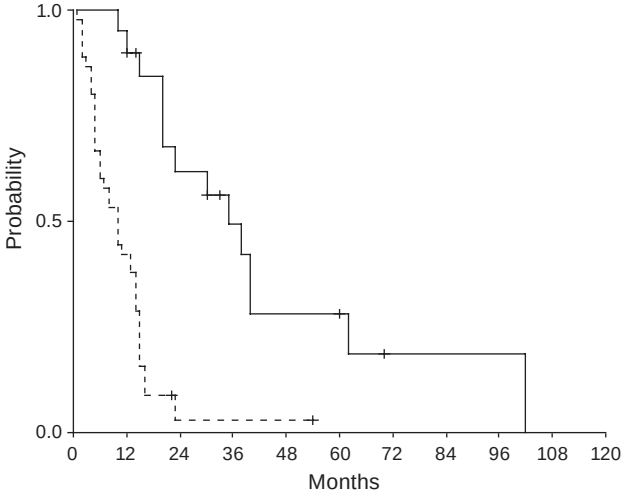

Figure 1. Overall survival curves by complete remission status.[CR (—), Non CR (– – –)]

Discussion

Despite advances in molecular immunohistochemistry and imaging technology, the diagnosis and therapy of patients with CUP remains a challenge [6]. A major advance in the field over the last decade was made by identifying the clinicopathological subsets of CUP patients with a more favourable prognosis. This allowed for tailoring of the therapeutic strategy towards more intensive modalities for good risk groups. Patients with midline nodal metastases as well as women with non-mucinous peritoneal carcinomatosis are thought to have entities equivalent to extragonadal germ cell cancer [7] and ovarian cancer [8] may respond to systemic platinum-based chemotherapy and occasionally enjoy long-term survival [4,5,7–11].

In our cohort most patients received platinum-based chemotherapy, commonly coupled with a taxane. Response rate was approximately 50%, among the highest reported to date, reproduced by a few authors using platinum-taxane regimens [3,12]. Antitumour activity was seen more commonly in women with peritoneal carcinomatosis (36% complete response rate), in contrast with complete response rates of 10–20% with platinum-alkylator regimens reported in the 1980s [13,14]. This difference translated into a 5-month absolute improvement of median survival for patients with

Table II. Response to chemotherapy.

	Peritoneal		Nodal		
	n (%)	95%CI	n (%)	95%CI	p-value[1]
CR	17 (36%)	22.7–51.5	3 (9%)	1.9–24.3	0.008
PR	8 (17%)	7.6–30.8	7 (21%)	9.0–38.9	
SD	8 (17%)	7.6–30.8	5 (15%)	5.1–31.9	
PD	7 (15%)	6.2–28.3	12 (36%)	20.4–54.9	
NE	7 (15%)	6.2–28.3	6 (18%)	7.0–35.5	
ORR	25 (53%)	38.1–67.9	10 (30%)	15.6–48.7	0.066

[1]p-values have been calculated using Fisher's exact test; CI = confidence interval; Values were rounded up. CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: non-evaluable, ORR: overall response rate.

Table III. Overall survival and time to progression (TTP), months.

	Peritoneal	Nodal	p-value*	All patients
Survival				
Events	34/41	28/29	0.0528	62/70
Median	15	10		14
95% CI	13–17	7–13		12–16
Range	1–102	2–54+		1–102
TTP				
Events	25/26	13/13	0.3891	38/39
Median	7	5		7
95% CI	5–9	3–7		5–9
Range	1–100	2–30		1–100
Median follow-up				60
95% CI				46–74
Range				1–102

*Log-rank test.

Table IV. Univariate prognostic factor analysis.

Univariate analysis for survival (significance level 0.05)			
	HR	95% CI	p-value
PS			
0–1	1		
2–3	1.3	0.76–2.12	0.332
Grade			
1–2	1		
3	1.47	0.83–2.60	0.191
Platinum-based chemotherapy			
No	1		
Yes	0.63	0.24–1.61	0.334
Group			
Peritoneal	1		
Nodal	1.62	0.97–2.71	0.066
Sex			
Male	1		
Female	0.60	0.35–1.04	0.069
Number of metastatic sites			
1–3	1		
>3	3.18	1.76–5.74	<0.001
CA 15-3			
Normal	1		
Abnormal	1.24	0.65–2.35	0.512
CA 125			
Normal	1		
Abnormal	0.51	0.30–0.87	0.014
CA 19-9			
Normal	1		
Abnormal	2.07	1.16–3.70	0.013
CEA			
Normal	1		
Abnormal	1.43	0.78–2.62	0.250

HR = hazard ratio; CI = confidence interval.

Table V. Multivariate prognostic factor analysis.

Multivariate analysis for survival (significance level 0.05)			
	HR	95% CI	p-value
Number of metastatic sites			
1–3	1		
>3	2.82	1.48–5.36	0.002
CA 125			
Normal	1		
Abnormal	0.53	0.29–0.95	0.032
CA 19-9			
Normal	1		
Abnormal	2.15	1.16–4.00	0.015

HR = hazard ratio; CI = confidence interval.

peritoneal carcinomatosis in comparison with nodal disease patients. These results during this time frame (1996–2002) are more favourable than those seen in most patients with metastatic adenocarcinoma of unknown primary involving multiple sites [1,3].

At first glance, the observed antineoplastic activity does not seem to translate into a considerable survival gain, with both progression-free and overall survival being stuck at a median interval of 5–15 months. Nevertheless, the minority of complete responders fared very well, achieving a striking median survival of 35 months. The presence of occasional long-term survivors among patients with peritoneal carcinomatosis in particular has to be stressed (5-year survival 10%). The outcome of such CUP patients is similar to those with bulky, suboptimally debulked stage III ovarian cancer (5-year survival 10–15%) in the platinum–taxane era and most investigators nowadays consider these as having primary peritoneal cancer rather than an unknown primary malignancy. On the other hand, patients with nodal disease fared worse than those with extragonadal germ cell tumours (5-year survival 30–40%) but the heterogeneity and high-risk profile of our nodal patient population is evident. Several authors have emphasized the potential inclusion of other entities such as undifferentiated lymphoma, carcinomas, and neuroendocrine tumours in the midline nodal group [15]. Indeed, in our nodal disease cohort, few patients had elevated serum levels of AFP or HCG, and their median age of 60 was higher than that described for typical extragonadal germ cell tumour patients, whereas more than a third had poor performance status [4]. Moreover, 36% of these patients were females.

These data lend weight to the reported heterogeneity and need for better classification of patients with midline nodal CUP. Overall, outcome data from our favourable CUP patient group also stress the need for therapeutic approaches to consolidate achieved remissions. Biological agents, rationally designed "smart" drugs, and maintenance chemotherapy have to be evaluated in this setting. Already epidermal growth factor receptor inhibitors, monoclonal antibodies against CA 125, and monthly taxanes for 12 months are being investigated [16,17].

In agreement with published data, factors significant for predicting outcome were presence of few metastatic sites, achievement of complete response, and bulk of disease [18,19]. There are contradictory data on the prognostic significance of administration of platinum-based chemotherapy in the medical literature. We failed to find any, again stressing the need for developing novel treatment approaches for these patients. The association of abnormal serum CA 125 levels with superior outcome may seem unexpected at first sight. However, elevated CA 125 levels may simply be a feature of presence of primary peritoneal, ovarian-type carcinoma, a disease with known chemosensitivity and occasional long-term survival, as opposed to women with normal CA 125 who do not really have this entity but rather undifferentiated peritoneal implants from a gastrointestinal primary.

Of note, ours is the only prognostic factor analysis performed in favourable CUP patients. However, the nature of the identified prognosticators raises doubt about their true prognostic ability, as they may simply represent characteristics of patient groups with more indolent, low-volume or chemosensitive malignancy from the outset (selection bias). Despite occasional cures, we are indeed a long way from understanding the behaviour and distinct characteristics of favourable CUP subsets and further insights into malignant developmental processes are needed. Molecular profiling by using DNA microarrays or other techniques offer some hope for unravelling this perplexing entity and for paving the way towards more effective therapies.

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