Pergamon

European Journal of Cancer Vol. 32A, No. 13, pp. 2357–2359, 1996
Copyright © 1996 Elsevier Science Ltd. All rights reserved
Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00346-2

Short Communication

Elevated Germ Cell Markers in Carcinoma of Uncertain Primary Site do not Predict Response to Platinum Based Chemotherapy

D.C. Currow,[1] M. Findlay,[2] K. Cox[2] and P.R. Harnett[1]

[1]Department of Medical Oncology and Palliative Services, The Nepean Hospital, P.O. Box 63, Penrith, NSW 2750; and [2]Department of Medical Oncology, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050, Australia

We carried out a retrospective review of the medical records of patients with metastatic carcinoma of unknown primary and either raised alpha fetoprotein (AFP) or beta human chorionic gonadotrophin (βHCG) over a period of 6 years at three teaching hospital oncology units to assess response to platinum based chemotherapy. 15 patients were identified who fitted these criteria. Of these, 3 received no treatment because of poor functional status, 2 patients received only radiotherapy for symptomatic disease and died within 3 months of diagnosis and 1 patient died 2 weeks after diagnosis having received his first cycle of cisplatin-based chemotherapy. 9 patients received at least 2 cycles of chemotherapy. A complete tumour response was seen in only one patient who presented with midline lymphadenopathy and remains disease-free 46 months after treatment. This presentation was consistent with disease already known to herald platinum sensitivity. In the other 8 patients, there was only one partial response that lasted 2 months. The median survival for this group of 9 patients was 4.5 months (range 3 to > 46 months). Our data do not support the postulate that elevated germ cell markers in patients with carcinoma of unknown primary predict a response to cisplatin based chemotherapy. Copyright © 1996 Elsevier Science Ltd

Key words: tumour marker, alpha fetoprotein, beta human chorionic gonadotrophin, neoploasm, unknown primary, platinum chemotherapy, germ cell

Eur J Cancer, Vol. 32A, No. 13, pp. 2357–2359, 1996

INTRODUCTION

METASTATIC CARCINOMA of uncertain primary (defined as patients with a biopsy proven metastatic carcinoma in whom a primary site is not demonstrated from the patient's history, physical examination, chest X-ray and urine analysis) remains a common clinical problem in oncological practice. The current approach to management is based upon the identification of potentially treatable subsets. These subsets have been defined largely by clinical presentation (e.g. axillary nodes in female patients, suggesting the presence of occult primary breast carcinoma).

Several previous studies suggest the existence of a subgroup of patients with poorly differentiated carcinoma who might derive a survival advantage from cisplatin based chemotherapy. In the earliest series, this group were often young males with mediastinal or retroperitoneal lymphadenopathy, sometimes in association with elevated beta human chorionic gonadotrophin (βHCG) or alpha fetoprotein (AFP) [1, 2]. This group of patients were labelled as having extragonadal germ cell tumours, and platinum based regimens were recommended. In a later series, higher response rates to platinum based chemotherapy have been reported for carcinoma of unknown primary patients with a histological subtype of poorly differentiated carcinoma [3, 4].

In the light of these reports, and the generally excellent responses to chemotherapy seen in testicular and ovarian germ cell tumours, we postulate that another chemoresponsive subtype may be carcinoma of unknown primary with an elevated germ cell marker (AFP or βHCG). Elevation of

Correspondence to D.C. Currow.
Received 17 Jun. 1996; accepted 12 Jul. 1996.

such markers could represent tumours that were unrecognised germ cell tumours, or germ cell type differentiation in extragonadal tumours. We, therefore, set out to determine the response rate according to World Health Organisation (WHO) criteria to chemotherapy in patients with carcinoma of unknown primary site with raised germ cell markers.

MATERIALS AND METHODS

In a retrospective review, the oncology charts and medical records of patients with carcinoma of unknown primary (according to the above definition) and raised AFP or βHCG diagnosed between January 1988 and December 1994 from three teaching hospital oncology centres were examined. Cases were found both through searching for carcinoma unknown primary on unit databases and through laboratory records of raised germ cell marker levels in non-pregnant patients' blood samples assayed in the participating hospitals.

AFP and βHCG were measured between 1988 and 1991 by radioimmunoassay (RIA). From 1991, they were measured on an ASXYM (Abbott) automated machine using microparticle enzymatic immunofluorescent assay (MEIA). Normal levels in non-pregnant people were < 8 IU/ml for AFP and < 10 mIU/ml for βHCG. For this study, abnormal levels were arbitrarily defined as being above a level of 80 IU/ml for AFP or 80 mIU/ml for βHCG.

RESULTS

15 patients with carcinoma of unknown primary were identified in whom βHCG or AFP was raised. Of these, 3 received no treatment because of poor functional status and intercurrent illness, all of whom died within 1–2 months of diagnosis. 2 other patients received radiotherapy alone for symptomatic disease and died within 3 months of diagnosis. One patient received one course of cisplatin, etoposide and bleomycin chemotherapy, but died 2 weeks after diagnosis from progressive disease.

The remaining 9 patients were evaluable for the purposes of this study, having received at least two cycles of chemotherapy. Their clinical characteristics and chemotherapy are summarised in Table 1. In summary, a complete tumour response was seen in only 1 patient who remains disease-free 46 months after treatment. This patient presented with midline lymphadenopathy, a pattern consistent with those previously described as heralding platinum sensitivity [5–7]. In the remainder of patients, who did not have this typical midline presentation, only one further partial response was seen lasting only 2 months. The median survival for this group of 9 patients overall was 4.5 months (range 3 to > 46 months).

DISCUSSION

Identification of a potentially treatable subset of patients with carcinoma of unknown primary remains a priority in oncological practice. Several previous studies suggest the existence of patient subsets who might derive a survival advantage from cisplatin based chemotherapy. These have typically been young males with mediastinal or retroperitoneal lymphadenopathy, although recent papers have suggested that this subgroup could be extended to patients with more atypical presentations [5, 8].

We postulated that the presence of raised βHCG or AFP may indicate either a germ cell origin of the tumour, or germ cell differentiation within the tumour, either of which might reasonably expect to be associated with chemosensitivity to cisplatin based treatment. In our series, 1 patient had typical midline lymphadenopathy. The remainder of the patients did not have a pattern of disease previously described as denoting platinum sensitivity. These patients showed no evidence of significant platinum sensitivity, and had a very poor median survival. Therefore, we find no evidence to suggest that raised germ cell markers in carcinoma of unknown primary, other than those patients presenting with extensive midline lymphadenopathy, indicate the presence of chemotherapy sensitive disease.

A review of the literature supports our contention [6, 7, 9–12]. In one of the first descriptions of the extragonadal germ cell tumour subgroup, 6 out of 12 patients had positive markers. Of these 6 patients, only one achieved a durable complete remission. By contrast, of the 6 patients who were marker-negative in this series, 4 were alive and

Table 1. Patients' characteristics

Age/sex	Pathology	Predominant site	Chemo*	Best response†	Survival (months)	Marker
50/M‡	Poorly differentiated carcinoma	Lung	4/0	PD	8.5	BHCG 93000
54/F	Undifferentiated large cell	Midline lymph nodes	5/0	PD	5	BHCG 82
32/M	Papillary adenocarcinoma	Liver	2/2	PD	6	BHCG 119
50/F	Large cell squamoid differentiated	Supraclavicular fossa	5/0	CR	>46	BHCG 7900
61/M	Squamous cell	Lung, psoas muscle	2/0	PD	5	BHCG 1800
28/F	Adenocarcinoma	Adnexal mass	1/3	PD	4	BHCG 555
29/M‡	Poorly differentiated adenocarcinoma yolk sac	Stomach	5/0	PR (2/12)	8	AFP 2800
56/M	Poorly differentiated adenocarcinoma	Liver	0/2	PD	4	AFP 39000
41/F	Adenocarcinoma	Pelvic mass	3/2	PD	3	AFP 1040

*Chemotherapy: number of complete cycles of platinum chemotherapy/number of complete cycles of non-platinum chemotherapy. †WHO criteria. ‡Had autologous bone marrow transplant. PD, progressive disease; CR, complete response; PR, partial response.

disease-free at a median of 9 months follow-up. The remaining 2 marker-negative patients had partial responses maintained over at least a 6 month period [9].

Greco and associates in a later series of 71 patients (incorporating the previously mentioned 12 patients) reported 15 complete responders to cisplatin based chemotherapy. Most patients in this series had tumour markers measured. Markers were raised in 13 patients. Of the 15 who did have a response to treament, only 2 had positive markers [10].

In a separate review of patients with carcinoma of unknown primary who responded to chemotherapy, only 3 out of 32 responding patients were marker-positive, and this was not found to be a positive predictor of survival [9]. Other subanalyses attempting to identify treatment of subsets of carcinoma of unknown primary have not revealed a positive marker as a favourable predictive feature [5, 7, 10].

7 patients included in another study of extragonadal germ cell tumours had poorly differentiated tumours with a pathology that may have been compatible with germ cell origin, elevated tumour markers and no obvious primary at diagnosis. All received conventional germ cell chemotherapy but none achieved a durable response despite good initial responses [11].

Pavlidis and associates reviewed six separate tumour markers in 85 patients with carcinoma of unknown primary. AFP was raised in 8 patients and βHCG in 15 patients. Neither marker predicted response to systemic chemotherapy, predominant site of disease nor the number of metastatic sites [12].

In our experience, the presence of markedly elevated germ cell markers is an uncommon phenomenon in patients with carcinoma of unknown primary. What is seen are identifiable primaries where AFP or βHCG may also be raised as has been reported for epithelial primary sites including carcinoma of the pancreas, stomach, oesophagus, bladder, biliary tree and lung [13].

Taken with our analysis of the available literature, our data do not support the postulate that elevated germ cell markers in patients with carcinoma of unknown primary predict a response to cisplatin based chemotherapy.

1. Fox RM, Woods RL, Tattersall MHN. Undifferentiated carcinoma in young men: the atypical teratoma syndrome. *Lancet* 1979, **1**, 1316–1318.
2. Greco FA, Oldham RK, Fer MF. The extragonadal germ cell cancer syndrome. *Semin Oncol* 1982, **9**, 448–455.
3. Hainsworth JD, Wright EP, Gray GF, Greco FA. Poorly differentiated carcinoma of unknown primary site: correlation of light microscopic findings with response to cisplatin-based combination chemotherapy. *J Clin Oncol* 1987, **5**, 1275–1280.
4. van der Gaast A, Verweij J, Henzen-Logmans SC, Rodenburg CJ, Stoter G. Carcinoma of unknown primary: identification of a treatable subset? *Ann Oncol* 1990, **1**, 119–122.
5. Hainsworth JD, Johnson DH, Greco FA. Cisplatin-based combination chemotherapy based treatment of poorly differentiated carcinoma and poorly differentiated adenocarcinoma of unknown primary site: results of a twelve year experience. *J Clin Oncol* 1992, **10**, 912–922.
6. Hainsworth JD, Dial TW, Greco FA. Curative combination chemotherapy for patients with advanced poorly differentiated carcinoma of unknown primary site. *Am J Clin Oncol* 1988, **11**, 138–145.
7. Maiche AG. Cancer of unknown primary. A retrospective study based on 109 patients. *Am J Clin Oncol* 1993, **16**, 26–29.
8. van der Gaast A, Verweij J, Planting AST, Hop WCJ, Stoter G. Simple prognostic model to predict survival in patients with undifferentiated carcinoma of unknown primary site. *J Clin Oncol* 1995, **13**, 1720–1725.
9. Richardson RL, Schoumacher RA, Fer MF, *et al.* The unrecognised extragonadal germ cell tumour. *Ann Int Med* 1981, **94**, 181–186.
10. Greco FA, Vaughan WK, Hainsworth JD. Advanced poorly differentiated carcinoma of unknown primary site: recognition of a treatable syndrome. *Ann Int Med* 1986, **104**, 547–553.
11. Logothetis CJ, Samuels ML, Selig DE, *et al.* Chemotherapy of extragonadal germ cell tumours. *J Clin Oncol* 1985, **3**, 316–325.
12. Pavlidis N, Kalef-Ezra J, Briassoulis E, *et al.* Evaluation of six tumour markers in patients with carcinoma of unknown primary. *Med Pediatric Oncol* 1994, **22**, 162–167.
13. Hainsworth JD, Greco FA. Poorly differentiated carcinoma and germ cell tumours. *Hematol Oncol Clin N Am* 1991, **5**, 1223–1231.