Eur J Cancer, Vol. 29A, No. 16, pp. 2217–2218, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Identification and Management of Poor Prognosis Germ Cell Tumours—a Need for Consensus

G. M. Mead

THE ACHIEVEMENT of cure for 80–85% of patients with metastatic germ cell tumour (GCT) treated with chemotherapy must rank as one of the greatest advances in modern oncology practice [1–3]. However, a small proportion of patients with germ cell cancers continue to die of their disease. The early recognition of these patients, and identification of new, more effective, therapeutic approaches, are priority areas for future clinical research.

Present evidence suggests that patients with metastatic GCT can be divided into two groups. Patients with advanced metastatic seminoma, together with those with good prognosis metastatic teratoma, form the great majority (70–80%) of patients receiving chemotherapy [3,4–8]. Current studies suggest that only 10–15% of such patients will fail if treatment with a recognised cisplatin, etoposide, bleomycin (BEP) [1,2] chemotherapy regimen is given. No definite criteria have yet been described by which this latter population can be identified.

The remaining patients with teratoma (approximately 20–30% of the GCT population) have a more adverse prognosis, with an anticipated 50–70% failure-free survival. Major efforts have been made to identify this population, and a number of phase II, and some phase III, chemotherapy trials have considered their best management.

These patients can be recognised in three ways. Identification at initial presentation is used most commonly, but it is probably the least sensitive and specific method. However, early introduction of a new therapeutic approach is perhaps most likely to increase cure rates. A wide variety of presenting prognostic criteria have been assessed including measurement of tumour bulk (utilising measurements of transverse or antero posterior tumour diameters at all sites [6,7]), tumour spread (number of sites [4], number of lung metastases [5–7], extent of visceral spread [6,7]) and tumour markers alpha fetoprotein (AFP), human chorionic gonadotrophin (HCG) [4,6–8] and lactate dehydrogenase (LDH) [4]. Other factors of probable importance are age and primary site (gonadal versus extragonadal). Surprisingly, no agreed prognostic factor classification is in use, and those available bear little relationship to each other, with a resultant spawning of literature comparing different systems [4,5,8]. Whilst inherently unsatisfactory, this situation has also rendered currently available phase II trials using new chemotherapy approachs difficult to interpret as almost all the inclusion criteria for each of these studies are different (inevitably always including a proportion of patients regarded as good prognosis by other classification systems) [8–13].

A potentially more specific way of identifying poor prognosis patients is by a dynamic evaluation of their response to therapy, most easily achieved by assessing rate of tumour marker decline—a subject of multiple studies during the last decade [14–16]. The Memorial Sloan Kettering Hospital group, at present, evaluate the rate of decline of AFP and HCG in poor prognosis patients treated with chemotherapy, and alter therapy if half lives prove prolonged [10,14]. However, this approach has not found widespread use, and has not been fully evaluated on independent data sets. The third and most obvious way of establishing a poor prognosis is by identification at the time of treatment failure. This can be achieved by including patients in whom active cancer is found at the time of resection of residual masses, those who fail to achieve marker complete remission, or those developing progression of cancer. Whilst specificity is high, it might be too late to bring in new therapeutic approaches—in almost all series the likely salvage rates for the latter two groups will not exceed 20%—and for patients with primary refractory disease are likely to be much lower than this.

How should patients with a poor prognosis at presentation be managed? There can be little doubt that the standard therapy, with which new approaches should be compared, is four to six cycles of BEP chemotherapy [1]. A wide variety of other chemotherapy regimens have been described and promoted [8,9,11–13], however, in the absence of randomised trials directed at this group it is difficult to recommend these. The Southeastern Cancer Study Group have compared standard BEP with BEP containing double-dose cisplatin [17], and more recently (and to date reported only in abstract form) with VIP (etoposide, ifosfamide and cisplatin) [18]. These two studies have demonstrated no increase in failure-free survival, but have documented markedly increased toxicity in the experimental treatment arm. The Medical Research Council/EORTC are currently comparing BEP with modified bleomycin, vincristine, cisplatin (BOP)/VIP(9)—the latter including both initial high dose intensity cisplatin and subsequent VIP and bleomycin—and are evaluating the role, if any, of filgrastim in this population.

Extrapolating from the studies conducted to date, it seems unlikely that enhancement of conventional dose chemotherapy will significantly improve cure rates. The advent of new means of circumventing haematological toxicity (growth factors, autologous bone marrow transplantation, peripheral stem cell transplantation) provides new opportunities for testing significantly more intensive treatment regimens. The clear demonstration that a proportion of patients failing multiple chemotherapy regimens can be cured with such high-dose therapy with autologous marrow support [19,20], and improved tolerance of this approach in less heavily pretreated patients [10], has lead to its earlier utilisation. The Indiana Group are currently testing dose-escalated chemotherapy as a component of first salvage treatment [21] (also the subject of an impending randomised European trial). High-dose therapy has also been tested in a French randomised trial as a component of initital therapy (with negative results [22]). It is of interest that 28% of patients in this trial who were randomised to transplantation failed to receive this therapy for a variety of reasons. The scrupulous study reported in this issue by Bokemeyer *et al.* (pp. 2225–2231) represents another thread of this approach. VIP has been given

Correspondence to G. M. Mead at the Department of Medical Oncology, Royal South Hants Hospital, Graham Road, Southampton SO9 4PE, U.K.
Received 4 Aug. 1993; accepted 1 Sep. 1993.

in dose escalated form by use of growth factor support—and a current study by this group aims to assess the potential, additional use of peripheral stem cell transplantation.

It seems likely that a proportion of patients with poor prognosis teratoma will remain incurable because of the catastrophic nature of their presentation [22,23]. However, for the remainder, there must be hope that results can be improved. It is becoming increasingly difficult to conduct pilot studies of new treatment approaches in this rare population—and these can only be tested by comparatively large studies likely to require international cooperation. A further difficulty is the toxicity and financial cost of many newer treatments.

An international collaborative effort is currently underway to define agreed, adverse prognostic factors. Similar cooperation is required in the future if we are to test new treatment approaches in randomised trials in these rare patient subgroups. Wherever possible, these patients should be included in clinical trials, or referred to centres participating in such studies. It seems likely that cure rates will improve, but progress may well be slow.

1. Williams SD, Birch R, Einhorn LH, *et al.* Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med* 1987, **316**, 1435–1440.
2. Dearnaley DP, Horwich A, A'Hern R, *et al.* Combination chemotherapy with bleomycin, etoposide and cisplatin (BEP) for metastatic testicular teratoma: long-term follow-up. *Eur J Cancer* 1991, **27**, 684–691.
3. Mencel P, Motzer RJ, Mazumdar M, *et al.* Chemotherapy (CT) for advanced seminoma: treatment results and survival in 143 patients. *Absract Proc ASCO* 1993, **12**, 233.
4. Bajorin D, Katz A, Chane E, *et al.* Comparison of criteria for assigning germ cell tumour patients to "good risk" and "poor risk" studies. *J Clin Oncol* 1988, **6**, 786–791.
5. Birch R, Williams S, Cone A, *et al.* Prognostic factors for favorable outcome in disseminated germ cell tumours. *J Clin Oncol* 1986, **4**, 400–407.
6. Mead GM, Stenning SP, Parkinson MC, *et al.* The second Medical Research Council study of prognostic factors in nonseminomatous germ cell tumours. *J Clin Oncol* 1992, **10**, 85–94.
7. Stoter G, Sleifer D, Kaye SB, *et al.* Prognostic factors in metastatic nonseminomatous germ cell tumours: an interim analysis of the EORTC GU-Group experience. *Eur Urol* 1993, **23**, 202–206.
8. Hitchins RN, Newlands ES, Smith DB, *et al.* Long-term outcome in patients with germ cell tumours treated with POMB-ACE chemotherapy: comparison of commonly used classification systems of good and poor prognosis. *Br J Cancer* 1989, **59**, 236–242.
9. Lewis CR, Fossa SD, Mead G, *et al.* BOP/VIP—a new platinum-intensive regimen for poor prognosis germ cell tumours. *Ann Oncol* 1991, **2**, 203–211.
10. Motzer RJ, Gulati SC, Crown JP, *et al.* High-dose chemotherapy and autologous bone marrow rescue for patients with refractory germ cell tumours. *Cancer* 1992, **69**, 550–556.
11. Logothetis CJ, Samuels ML, Selig D, *et al.* Improved survival with cyclic chemotherapy for nonseminomatous germ cell tumors of the testis. *J Clin Oncol* 1985, **3**, 326–335.
12. Harstick A, Schmoll HJ, Kohn-Wompner CH, *et al.* Cisplatin, etoposide, ifosfamide, vincristine and bleomycin combination chemotherapy for far advanced testicular carcinoma. *Ann Oncol* 1991, **2**, 197–202.
13. Dangaard G, Rorth M. Treatment of poor-risk germ-cell tumours with high-dose cisplatin and etoposide combined with bleomycin. *Ann Oncol* 1992, **3**, 277–282.
14. Toner GC, Geller NL, Tan C, *et al.* Serum tumour marker half-life during chemotherapy allows early prediction of complete response and survival in nonseminomatous germ cell tumours. *Cancer Res* 1990, **50**, 5904–5910.
15. Vogelzang NJ, Lange PH, Goldman A, *et al.* Acute changes of α-fetoprotein and human chorionic gonadotrophin during induction chemotherapy of germ cell tumours. *Cancer Res* 1982, **42**, 4855–4861.
16. Picozzi VJ, Freiha FA, Hannigan JF, *et al.* Prognostic significance of a decline in serum human chorionic gonadotrophin levels after initial chemotherapy for advanced germ-cell carcinoma. *Ann Int Med* 1984, **100**, 183–186.
17. Nichols CR, Williams SD, Loehrer PJ, *et al.* Randomised study of cisplatin dose intensity in poor-risk germ cell tumors: a Southeastern Cancer Study Group and Southwest Oncology Group protocol. *J Clin Oncol* 1991, **7**, 1163–1172.
18. Loehrer PJ, Einhorn LH, Elson SD, *et al.* Phase II study of cisplatin (P) plus etoposide (VP16) with either bleomycin (B) or ifosfamide (I) in advanced stage germ cell tumors (GCT): an intergroup trial. *Abstract Proc ASCO* 1993, **831**, 261.
19. Nichols CR, Anderson J, Lazarus HM, *et al.* High-dose carboplatin and etoposide with autologous bone marrow transplantation in refractory germ cell cancer: an Eastern cooperative oncology group protocol. *J Clin Oncol* 1992, **10**, 558–563.
20. Droz JP, Pico JL, Ghosn M, *et al.* Long-term survivors after salvage high-dose chemotherapy with bone marrow rescue in refractory germ cell cancer. *Eur J Cancer* 1991, **27**, 831–835.
21. Broun ER, Nichols CR, Turns M, *et al.* First line salvage therapy and high dose chemotherapy with autologous bone marrow rescue (ABMR) for germ cell cancer. *Abstract Proc ASCO* 1993, **12**, 792.
22. Chevreau C, Droz JP, Pico JL, *et al.* Early intensified chemotherapy with autologous bone marrow transplantation in first line treatment of poor risk non-seminomatous germ cell tumours. *Eur Urol* 1993, **23**, 213–218.
23. McKendrick JJ, Theaker J, Mead GM. Non-seminomatous germ cell tumour with very high serum human chorionic gonadotrophin. *Cancer* 1991, **67**, 684–689.

Eur J Cancer, Vol. 29A, No. 16, pp. 2218–2220, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

To Screen or Not to Screen for Cervical Cancer

Matti Hakama

SCREENING FOR cervical cancer may succeed or fail for a number of disparate reasons. On the one hand, it may fail for reasons associated with the natural history of the disease; a screening test should be able to identify a preclinical phase of the disease, at which treatment is more efficacious than at later clinical stages. On the other hand, it may fail because of medico-socio reasons, including errors by those providing, planning or executing medical services, or by those receiving such services.

In any successful screening programme (i.e. a programme which results in a reduction of invasive cancer or death from cervical cancer), both the natural history (biology) of cervical cancer and the organisation of screening medical services must fulfil the general prerequisites for a successful screening. The programme works as well as its weakest link. Thus, there are

Correspondence to M. Hakama at the Department of Public Health, University of Tampere, Tampere, and the Finnish Cancer Registry, Helsinki, Finland.
Revised 14 June 1993; accepted 29 June 1993.