Eur J Cancer, Vol. 29A, No. 7, pp. 933–934, 1993.
Printed in Great Britain

0964-1947/93 $6.00 + 0.00
Pergamon Press Ltd

Comments and Critique

Current Issues in the Management of Clinical Stage I Testicular Teratoma

THE EVOLUTION of management concepts in stage I testicular teratoma reflects the impact of curative chemotherapy, which was developed in the 1970s by Samuels *et al.* [1], Einhorn and Donohue [2] and Peckham *et al.* [3, 4]. In the current era standard combinations of bleomycin, etoposide and cisplatin (BEP) will cure approximately 85% of all patients presenting with metastatic testicular non-seminoma, and this proportion increases to upward of 94% in those with a limited extent of metastatic disease [5–10].

The effectiveness of chemotherapy on metastases has allowed stage I testicular teratoma to be freed from the concept of "radical loco-regional therapy". In the past it was necessary to base therapy on the ablation of any possible subclinical spread to retroperitoneal lymph nodes, since persisting disease in these sites would eventually lead to more widespread dissemination and death. Thus the mainstays of management postorchidectomy were either retroperitoneal lymph node dissection (RPLND) or retroperitoneal radiotherapy (RT). Either was effective in controlling retroperitoneal disease especially in the era of modern radiological staging when large volume retroperitoneal nodes were unlikely to be missed. Both of these management policies do, however, have disadvantages, including the 10–15% failure rate in patients with subclinical thoracic disease and also specific toxicity such as bone marrow suppression after radiotherapy or failure of ejaculation after surgery. In the light of modern chemotherapy and of alternative treatment strategies, radiotherapists, to their credit, have virtually abandoned their role in stage I teratoma, yet many urological surgeons still feel that RPLND is the optimal management postorchidectomy, partly because of its contribution to accurate staging of the retroperitoneum and partly because of the improvements in technique which have allowed a reduced risk of ejaculatory failure.

Surveillance after orchidectomy was introduced by Peckham in 1979 as an alternative to adjuvant therapy [11] based on the perception that small volume relapse would be curable with chemotherapy, and that surveillance would spare two-thirds of patients any further treatment. These predictions have been confirmed in multicentre studies [12, 13]. It is clear that the majority of oncology centres can pursue this management policy competently, and it is also clear that the patients' survival probability on surveillance is equivalent to that with any other approach to stage I non-seminoma. Furthermore, since surveillance is based on allowing expression of the natural history of the disease, failure analysis has allowed prospective definition of pretreatment risk factors [12, 14]. The U.K. Medical Research Council (MRC) Group originally reported a retrospective study in which multivariate analysis identified four independent histological risk factors, namely, invasion of testicular veins, invasion of testicular lymphatics, the presence of undifferentiated (embryonal) cells and the absence of yolk sac elements [12]. Subsequently, a prospective study of surveillance in 366 patients supported the use of a prognostic index based on these four factors, which indicated that patients with at least three of the factors had a 46% risk of relapse, compared to 21% for two factors, 16% for one factor and there were no relapses in the 9 patients with no risk factors [13].

The identification of a high-risk group on surveillance has stimulated further evolution of the role of chemotherapy, which is now being investigated as an adjuvant in high-risk clinical stage I teratoma. The MRC Group initiated an adjuvant chemotherapy programme in these patients in 1987 based on the use of only two cycles of BEP chemotherapy. The policy has been reported in abstract [15] with results, based on 61 patients registered by December 1991. This indicated that no patients had relapsed, though 1 has since relapsed. This level of effect of adjuvant chemotherapy was equivalent to that reported when two cycles of chemotherapy were employed following RPLND of pathological stage II non-seminoma [16].

Discussions of adjuvant chemotherapy in clinical stage I non-seminoma have included issues such as definition of the high risk group and also choice of chemotherapy regimen. There is concern that the good prognostic influence of yolk sac elements within the primary may relate to an association with raised serum concentration of alpha-fetoprotein (AFP). The long physiological half-life of this protein in the serum leads to a longer delay between orchidectomy and registration for surveillance. In the prospective MRC surveillance study a time of more than 3 weeks between orchidectomy and normalisation of markers was associated with a lower 2-year recurrence rate [13]. A second problem was that many pathologists felt there was difficulty in truly distinguishing venous from lymphatic invasion in the testis. Thirdly, if the high risk group definition is confined to patients with at least three risk factors this identifies less than half of those destined to relapse. In the MRC Group Study the high risk group comprised 83 of 366 patients, thus adjuvant chemotherapy had only a minor impact on the overall pattern of care and incidence of recurrence. In practice, therefore, it seems likely that future studies will be based on a simpler and more prevalent definition such as any vascular invasion (either venous or lymphatic).

A second issue to consider in the adjuvant chemotherapy of clinical stage I non-seminoma is the ideal chemotherapy regimen.

Correspondence to A. Horwich at the Urological Oncology Unit, The Royal Marsden Hospital, and Section of Radiotherapy, Institute of Cancer Research, Downs Road, Sutton, Surrey, U.K.
Received 17 Dec. 1992; accepted 18 Dec. 1992.

Since a significant proportion of treated patients would have been cured prior to chemotherapy it is important to minimise toxicity, and even though two cycles of BEP have negligible long-term side-effects it may be possible to reduce short-term morbidity significantly by the avoidance of alopecia and of prolonged in-patient therapy. These aims might be achieved by substituting etoposide with vincristine, and cisplatin with carboplatin. However, any such approaches need careful evaluation to ensure there is no significant compromise of efficacy, since inadequate initial chemotherapy may lead to drug-resistant relapse.

The article in this issue by Droz and van Oosterom reviews stage I non-seminoma of the testis with a particular focus on the issues to be considered in designing a pan-European prospective randomised trial in this stage of the disease. The worthy goal is to compare surgery, surveillance and adjuvant chemotherapy. A particular problem is the excellent prognosis for all modalities with survival probabilities of > 95%, and with little possibility of there being > 2% difference between the modalities. This makes it impossible to consider a survival endpoint for a prospective comparative trial, especially since the disease is uncommon. The endpoints of any trial must, therefore, be based on toxicity and quality of life measures; also, socioeconomic factors are an important influence [17]. An American study has suggested that the major toxicity influencing quality of life is loss of ejaculation [18], but since this is associated only with RPLND a comparative trial is hardly needed for this endpoint. Furthermore, this toxicity relates to individual surgical experience and skill, especially since the introduction of nerve sparing techniques. At the same time both surveillance programmes and adjuvant chemotherapy schedules are being refined as discussed above. Possibly, progress in the management of clinical stage I testicular non-seminoma will be based on optimising each of the approaches individually, rather than attempting to prove that one of them is best.

Alan Horwich
Urological Oncology Unit
The Royal Marsden Hospital, and Section of Radiotherapy
Institute of Cancer Research
Downs Road
Sutton, Surrey, U.K.

1. Samuels ML, Lanzotti VJ, Holoye PY, Boyle LE, Smith TL, Johnson DE. Combination chemotherapy in germinal cell tumor. *Cancer Treat Rev* 1976, 3, 185–204.
2. Einhorn LH, Donohue, J. *Cis*-diammine-dichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann Intern Med* 1977, 87, 293–298.
3. Peckham MJ, Barrett A, McElwain TJ, Hendry WF. Combined management of malignant teratoma of the testis. *Lancet* 1979, ii, 267–270.
4. Peckham MJ, Barrett A, Liew K, *et al.* The treatment of metastatic germ-cell testicular tumours with bleomycin, etoposide and *cis*-platinum (BEP). *Br J Cancer* 1983, **47**, 613–619.
5. Peckham MJ, Horwich A, Easton DF, Hendry WF. The management of advanced testicular teratoma. *Br J Urol* 1988, **62**, 63–68.
6. 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.
7. Williams SD, Birch R, Einhorn LH, Irwin L, Greco FA, Loehrer PJ. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin and either vinblastine or etoposide. *N Engl J Med* 1987, **316**, 1435–1440.
8. Pizzocaro G, Piva L, Salvioni R, Zanoni F. Milani A. Cisplatin, etoposide, bleomycin first-line therapy and early resection of residual tumor in far-advanced germinal testis cancer. *Cancer* 1985, **56**, 2411–2415.
9. Horwich A, Dearnaley DP, Nicholls J, Jay G, Mason M, Harland S. Effectiveness of carboplatin, etoposide, bleomycin (CEB), combination chemotherapy in good prognosis metastatic testicular non seminomatous germ cell tumours. *J Clin Oncol* 1991, **9**, 62–69.
10. 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.
11. Peckham MJ, Barrett A, Husband JE, Hendry WF. Orchidectomy alone in testicular stage I non-seminomatous germ-cell tumours. *Lancet* 1982, ii, 678–680.
12. Freedman LS, Parkinson MC, Jones WG, *et al.* Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchidectomy alone. *Lancet* 1987, ii, 294–298.
13. Read G, Stenning SP, Cullen MH, *et al.* Medical Research Council prospective study of surveillance for stage I testicular teratoma. *J Clin Oncol* 1992, **10**, 1762–1768.
14. Hoskin P, Dilly S, Easton D, Horwich A, Hendry WF, Peckham MJ. Prognostic factors in stage I non seminomatous germ cell testicular tumours managed by orchiectomy and surveillance: implications for adjuvant chemotherapy. *J Clin Oncol* 1986, **4**, 1031–1036.
15. Cullen MH, Stenning S, Fossa SD, Horwich A, Kaye SB, MRC TTWP. Short course adjuvant chemotherapy in high risk stage I non-seminoma germ cell tumours of the testis (NSGCTT): preliminary report of an MRC study. *Br J Cancer* 1992, **65** (suppl. XVI), 8.
16. Williams SD, Stablein DM, Einhorn LH, *et al.* Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. *N Engl J Med* 1987, **317**, 1433–1438.
17. Moynihan C. Psychosocial assessments and counselling of the patients with testicular cancer. In Horwich A, ed. *Testicular Cancer—Clinical Investigation and Management*. London, Chapman and Hall Medical, 1991, 353–368.
18. Rieker PP, Edbril SD, Garnick MB. Curative testis cancer therapy: psychosocial sequelae. *J Clin Oncol* 1985, 3, 1117–1126.

Acknowledgements—Supported by grants from the Cancer Research Campaign and the Bob Champion Cancer Trust.