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Editorial

Current Status of Chemotherapy in Advanced Seminoma

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AT DIAGNOSIS, approximately 80% of patients with pure testicular seminoma present with no evidence of metastases (Stage I). Approximately 1–3% of these patients relapse after abdominopelvic radiotherapy, as do 20% of patients managed by the alternative policy of surveillance. Pure seminoma is one of the most radiosensitive tumours known in oncology, and radiotherapy will be curative in a substantial proportion of patients with stage II disease and limited retroperitoneal lymph node metastases [1–4]. Controversy exists about the size of retroperitoneal tumour which can safely be irradiated with optimal survival rates and minimal long-term toxicity. However, in patients with retroperitoneal lymph node metastases >5 cm (stage IIc) and in patients with stage III/stage IV disease, most oncologists prefer to treat them initially with chemotherapy because of the high sensitivity of these germ cell tumours to platinum-based chemotherapy [5–12].

A number of features of the tumour biology and presentation of advanced seminoma are of fundamental importance in the clinical management of this condition and are laid out below.

CLINICAL PRESENTATION AND TUMOUR BIOLOGY

Firstly, patients with seminoma are, in general, 6–8 years older than non-seminoma patients, with approximately 15% above the age of 50 years. Due to the age-related decrease of renal and bone marrow function and the presence of concomitant chronic diseases, such as cardiovascular disorders, the risk of chemotherapy-related life-threatening toxicity is higher than in the younger patients with non-seminoma. Particular attention is, therefore, required regarding selection and dosage of the cytotoxic drugs in these patients, and individualisation of treatment schedules is often required. Secondly, the prognosis of patients relapsing after radiotherapy is often worse than that of non-irradiated patients with a similar extent of the disease, although these differences usually have not reached a level of statistical significance [6, 13]. Early in the 1980s, these findings may have been a consequence of the frequent dose reductions which were necessary in patients who had undergone treatment with the large-field infra- and supradiaphragmatic radiotherapy fields in use at that time. This dose-limiting effect of prior radiotherapy is not evident in patients who have undergone moderate dose infradiaphragmatic radiotherapy only [7]. In particular, there is no evidence for an increased failure rate of salvage treatment in patients relapsing after modern radiotherapy of stage I seminoma. Thirdly, the combination of radiotherapy and intensive chemotherapy should be avoided whenever possible due to the increased risk of acute and particularly long-term toxicity including induction of second malignancies [14–16; for [16] see pages 244–252].

SELECTION OF DRUGS

Cisplatin monotherapy yields progression-free survival rates of approximately 75% [17]. The combination of cisplatin with vinblastine or etoposide and bleomycin leads to progression-free survival rates of approximately 85% [5–10]. Because of the risk of pulmonary toxicity, bleomycin has been omitted completely from several drug combinations or has been substituted by alkylating agents such as cyclophosphamide or ifosfamide [18, 19]. In order to reduce the treatment-related toxicity furthermore, carboplatin has been introduced in the treatment of advanced seminoma [11,12].

Phase II studies with carboplatin monotherapy have indicated progression-free survival rates of 80–90%. A U.K. Medical Research Council phase III trial compared single agent carboplatin with the combination of cisplatin and etoposide and recruited 130 patients between August 1990 and January 1994 [20]. The trial was prematurely closed, at least in part, because of concerns about the inferior activity of carboplatin when used in combination chemotherapy for non-seminomatous tumours. It was concluded that cisplatin/etoposide should remain the standard combination treatment in advanced seminoma, although no survival difference was apparent between the two arms in this relatively small study. A similar German trial continues to compare single agent carboplatin with a combination of ifosfamide, cisplatin and etoposide.

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MANAGEMENT OF RESIDUAL POSTCHEMOTHERAPY MASSES

As with non-seminoma, residual masses at the sites of metastases quite often occur after chemotherapy of seminoma, especially in the retroperitoneal space. Ninety per cent of these masses contain fibrosis only [21–23]; the finding of mature teratoma is extremely rare. Puc and associates [22] found that the risk of residual malignant tumour was particularly high in persistent masses >3 cm in diameter, and these authors recommended the routine resection of residual tumours of such size. Other authors have not been able to confirm these findings [21, 23]

The demonstration of pure fibrosis in 9 of 10 postchemotherapy masses means that the overwhelming majority of seminoma patients would undergo a major operation unnecessarily if postchemotherapy surgery were routine. In addition, postchemotherapy surgery in these patients is associated with a higher risk of postoperative complications than is encountered in patients with non-seminoma [6]. Currently, routine postchemotherapy surgery is not recommended in patients with seminoma. Most clinicians prefer to observe residual masses after cisplatin-based chemotherapy and consider local consolidation treatment only if a persistent mass increases in size or large tumour masses persist after $\geqslant 6$ months without size reduction. The resection of such masses is recommended. If this is not possible, a biopsy should be performed and treatment with radiotherapy reserved for cases with histologically demonstrated viable malignancy. Because of the increased risk of second cancer if intensive chemotherapy is combined with irradiation, such postchemotherapy radiotherapy should be given to limited fields and at moderate doses. After single-agent carboplatin treatment, postchemotherapy–radiotherapy may be required more often than after the use of cisplatin combinations [24].

PROGNOSTIC FACTORS

The definition of prognostic groups in advanced seminoma may help the clinician to establish the optimal balance between efficacy and risk of toxicity during treatment of the individual patient with advanced seminoma. The IGCCCG (International Germ Cell Cancer Cooperative Group) reviewed 637 patients treated with chemotherapy for advanced seminoma and demonstrated 3-year survival in 82% [25]. Those with liver, bone and brain involvement had a 77% 3-year survival probability compared with 86% for those without metastases at these sites. If all germ cell tumours were considered together, then elevated serum lactate dehydrogenase (LDH) ($>1.5 \times N$) represented an adverse prognostic factor. In multivariate analysis, the presence of non-pulmonary visceral metastases and an elevated serum LDH represented independent adverse factors. A more detailed analysis of 286 of the above 637 patients confirmed these independent prognostic factors [26] as also identified by Mencel and associates [13]. Mencel and associates have also found that an elevated pretreatment serum HCG correlates with poor outcome. Though older studies have indicated previous radiotherapy as an adverse prognostic factor, this seems less relevant for patients relapsing after modern treatment of stage I seminoma [26; see pages 253–262].

CONCLUSION

Cisplatin-based combination chemotherapy represents the treatment of choice in the majority of patients with advanced seminoma. Due to the age and general condition in patients, individualised treatment is often necessary based on an awareness of prognostic factors. The presence of non-pulmonary visceral metastases and an elevated serum LDH represent independent adverse factors for progression-free survival. Postchemotherapy surgery is only necessary occasionally, but should be considered in young patients with persistent or increasing masses, particularly after the use of carboplatin monotherapy. The combination of intensive chemotherapy and large-field radiotherapy should be avoided.

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