indications for BMT but randomised studies are needed to show whether BMT is the best available strategy for this group of patients.

CONCLUSIONS AND PROSPECTIVES

Indications for BMT in non Hodgkin lymphomas as reviewed in this paper can lead to 2000 or 3000 BMT every year in the USA. Randomised studies are needed to convince the medical community and also . . . insurance companies. In December 1990:

— Randomised studies are necessary and welcome. They should all be considered as high priority.

— PR with positive biopsy and sensitive relapses are the only group of patients in which BMT may be the best therapy available for diffuse lymphomas, despite the lack of proof with prospective studies.

— Primary refractory patients and resistant relapses are not good indications and should be a group eligible for phase II studies.

— Non-randomised studies in CR1 are probably unethical and certainly unwise.

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Current Controversies in the Management of Testicular Cancer

A. Horwich

INTRODUCTION

TESTICULAR CANCER is important to oncology not only as a model of a curable tumour, but also because of the relatively young age of presentation, the rising incidence, the expression of sensitive and relatively specific tumour markers and the contribution of the high proportion of surviving patients to knowledge of late treatment toxicity. The vast majority of both seminomatous and non-seminomatous tumours are associated with carcinoma *in situ* (CIS) of the testis, a lesion also found in 0.5%–1.0% of infertile men, 5% of contralateral testes in patients with testicular germ cell tumours, 50% of extragonadal germ cell tumour presentations and nearly all cases of gonadal dysgenesis [1]. Follow-up has suggested that CIS progresses to invasive tumour at a rate of approximately 50% of cases within 5 years [2], forming either seminoma or non-seminoma. Carcinoma *in situ* is an aneuploid lesion and seminoma has a modal chromosome number of 60–69, non-seminoma 50–59 and combined tumours a number in between these two [3, 4].

The great majority of germ cell tumours have an isochromosome of the short arm of chromosome 12 [5]. The Kirsten *RAS* oncogene is on chromosome 12p and the formation of the isochromosome thus amplifies c-Kirsten-*RAS*. However, the relevance of this to prognosis is unclear. Non-seminomatous tumours also have a high frequency of chromosome 1 abnormalities [3, 6].

MANAGEMENT OF CIS

This premalignant lesion is found in approximately 5% of contralateral testes sampled at the time of orchidectomy for germ cell tumour [2]. The incidence of CIS is increased in patients with an atrophic contralateral testis or in patients with a history of testicular maldescent. The fact that 50% of CIS lesions progress to invasive tumour within 5 years has led to the advocacy of routine contralateral testicular biopsy to diagnose CIS [7]. An alternative approach is to consider biopsy only in patients with one of the predisposing risk factors.

Once CIS of the contralateral testis is diagnosed, options for management include observation, orchidectomy, or low dose testicular radiation. Preliminary evidence would suggest that long-term control of CIS by systemic chemotherapy is uncertain [8]. In the past, this lesion has not been diagnosed and thus the contralateral testis has, of necessity, been managed by observation. 2–5% of patients do develop a new germ cell tumour of the contralateral testis, however, the excellent prognosis of

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patients with germ cell tumours has led to relatively little impact of a second tumour on overall survival. The disadvantage of surveillance is that the development of second tumours necessitates second orchidectomy with problems of infertility and hormone replacement. An immediate orchidectomy following diagnosis of CIS obviously shares these side-effects. An alternative which has recently been proposed [9] is to treat CIS of the contralateral testis with low dose testicular irradiation. There has been some experience that a dose of 20 Gy in 10 fractions over 2 weeks eradicates CIS. Though early information suggested that this dose did not affect hormone production by the testis, recent studies have raised some doubt over this contention and the ideal radiation dose to prevent relapse of CIS yet not impair testicular hormone production has yet to be established. 20 Gy is certainly a dose high enough to cause sterility; however, most patients with CIS of the testis have, in any event, a low sperm count. The Royal Marsden policy is to offer contralateral testicular biopsy to patients with a history of maldescent or with an atrophic contralateral testis and if CIS is diagnosed, to offer either observation, especially if the patient has sperm production (and plans a family); or alternatively, low dose testicular irradiation to a total dose of 18 Gy in 9 fractions over 2 weeks.

SEMINOMAS

Stage I seminoma

The traditional management following orchidectomy is retroperitoneal node irradiation to a field encompassing para-aortic and ipsilateral pelvic nodes. The relatively low dose of radiotherapy of 30 Gy in 15–20 fractions over 3–4 weeks is well tolerated and it has been difficult to document reliably any long term side-effects of this treatment [10]. The risk of relapse is approximately 2% [11]. It is unlikely that an alternative management policy could improve recurrence or cure rates. However, concern over the possibility of radiation-induced second tumours has made it appropriate to investigate the need for adjuvant radiotherapy and a number of centres have therefore examined a policy of surveillance in stage I seminoma [10, 12, 13]. They have demonstrated that approximately 15% of patients defined as stage I on clinical and radiological investigation do in fact have subclinical metastatic disease very predominantly within para-aortic lymph nodes and revealed by relapse on surveillance. The great majority of recurrences have occurred within 4 years of orchidectomy though long term follow-up of this management approach has not yet been reported. The absence of a reliable and sensitive serum marker for seminoma has made this a difficult policy to carry out and the difficulty is compounded by the slow natural history of seminoma leading to a requirement for prolonged surveillance. Surveillance is no longer being carried out routinely at the Royal Marsden Hospital where the current policy is to support the Medical Research Council Testicular Tumour Working Party prospective randomised field size trial comparing standard para-aortic and pelvic radiotherapy with para-aortic field alone.

Metastatic seminoma

Recurrence rates are high after radiotherapy alone for bulky stage II, stage III and stage IV disease [14]. There is some controversy over the extent of abdominal disease which is appropriately managed by initial radiotherapy. Most chemotherapy reports on advanced seminoma have included patients with abdominal masses 5 cm or more in diameter; however, it has been argued that radiotherapy results for stage II disease with lymph node masses less than 10 cm in diameter are extremely good and that this represents a less toxic management than combination chemotherapy [15].

A range of reports has indicated the chemosensitivity of these tumours to regimens containing cisplatin [16–19]. It has also been suggested that single agent therapy may be as effective in seminoma as combination chemotherapy [20, 21]. A recent report on single agent carboplatin [22] indicated that 80% of 33 patients with advanced seminoma remained free from progression after a median follow up of 2 years. The current Medical Research Council trial in advanced seminoma is prospectively comparing single agent carboplatin with the combination of etoposide and cisplatin in patients with stage IIC (abdominal mass more than 5 cm in transverse diameter), stage III and stage IV metastatic testicular seminoma.

Residual mass after chemotherapy of advanced seminoma

In patients treated with cisplatin-based chemotherapy for advanced seminoma, a residual mass is found at the site of original disease in about two thirds of patients when response is assessed by computer tomographic (CT) scanning [17]. It has been claimed that residual masses more than 3.5 cm in diameter are particularly likely to contain residual active seminoma [23]. However, other reports have not confirmed that recurrences occur in particular from these residual masses [22, 24]. The role of adjuvant radiotherapy following chemotherapy has not been established. However, in patients with stage II presentations adjuvant radiotherapy can be to a limited field and carries little morbidity. A reasonable approach to the residual mass is to follow it by sequential CT scans every 3 months. Resection of these masses can be hazardous due to vascular complications; however, a mass which does not regress for 6 months following completion of chemotherapy should be biopsied to determine the indications for radiotherapy or further chemotherapy.

NON-SEMINOMAS

Stage I non-seminoma

A number of clinical approaches have been successful in curing patients with stage I non-seminoma of the testis [25]. These have included retroperitoneal lymph node dissection (RPLND) and deferred chemotherapy, RPLND and routine adjuvant chemotherapy, radiotherapy with chemotherapy deferred for relapse, or surveillance with chemotherapy deferred for relapse. The perceived advantages of RPLND include improved accuracy of staging partly due to the presence of subclinical metastases in normal sized lymph nodes but also due to a small proportion of patients with lymphadenopathy who do not have metastatic disease. Additionally, for patients with the earliest evidence of metastatic disease, the node dissection may itself be curative in 60–75% of cases, whereas the surgical demonstration of extensive node involvement is associated with a high recurrence rate that may in itself provide an indication for immediate adjuvant chemotherapy [26]. Patients shown histologically to be free from lymph node metastases have a relapse rate of only 10–20% mainly in the lungs and on relapse these patients are managed by combination chemotherapy. Patients with histological evidence of retroperitoneal node involvement have been managed either by surveillance or by immediate adjuvant chemotherapy and a prospectively randomised trial in patients with surgically staged II disease comparing surveillance with 2 cycles of cisplatin-based chemotherapy demonstrated the efficacy of the latter approach [26]. Of the 195 evaluable patients, the recurrence rate on the surveillance arm

was 49% with 3 deaths from disease whereas following adjuvant chemotherapy, there were only 6 recurrences (6%), 5 of which were in patients who had not received the assigned adjuvant treatment.

The major disadvantage of RPLND has been induction of dry ejaculation caused by autonomic nerve dissection in the region of the aortic bifurcation. Recently techniques of more limited node dissection have been developed [27–29]. These appear to produce accurate staging information and surgeons experienced in these techniques can avoid the side-effect of dry ejaculation. Nevertheless, it is clear that retroperitoneal node dissection represents major surgery and for two thirds of patients with clinical stage I non-seminoma of the testis, the procedure can retrospectively be determined to have been unnecessary since they did not have metastatic disease.

An alternative management policy for clinical stage I non-seminoma is surveillance. This policy was introduced at the Royal Marsden Hospital in 1979. It has subsequently been evaluated in a multicentre study coordinated by the Medical Research Council [30]. Of 259 patients managed by surveillance, the 4 year actuarial risk of relapse was 32% (95% confidence intervals, 25–40%). Patients who relapse on surveillance can be treated successfully with combination chemotherapy and the overall 3 year survival probability was 98.5%. This is clearly equivalent to that achieved by node dissection.

A third possibility in the management of clinical stage I non-seminoma is immediate treatment with adjuvant chemotherapy. This has not been explored extensively but is becoming a more realistic proposition because of the current ability to reduce the toxicity of chemotherapy and also because of the information from the post lymphadenectomy study that 2 courses of adjuvant chemotherapy are sufficient to control subclinical amounts of disease [26]. This management policy may be even more relevant if patients with stage I non-seminoma at a high risk of relapse can be identified. Information both from surveillance studies and from lymphadenectomy series suggest that the presence of lymphatic and vascular invasion within the primary tumour indicates a high risk of metastatic disease [31, 32]. The Medical Research Council has developed a prognostic index based on the following four factors: vascular invasion, lymphatic invasion, undifferentiated cells, and absence of yolk sac elements.

The presence of any 3 of these factors indicates a relapse risk of approximately 50% [30] and constitutes an indication for adjuvant chemotherapy using 2 courses of bleomycin, etoposide, cisplatin (BEP) chemotherapy [33].

The management decision in clinical stage I non-seminoma is unlikely to influence survival and will depend upon the resources and expertise available at the centre managing the patient. A cure rate of more than 95% should be anticipated.

Metastatic non-seminoma: prognostic classification

With modern platinum-based chemotherapy schedules 80–90% of patients with metastatic non-seminoma are cured [34]. Prognostic factor analyses have allowed stratification of patients into a good prognosis subgroup when the future challenge is to develop less toxic treatments, or into a relatively poor prognosis subgroup where the aim is to increase the efficacy of chemotherapy. There is some controversy over the definition of these subgroups which relates to the appropriate treatment decision. Thus if prognostic classification defines a group with a 25% chance of survival, this would merit a very aggressive management approach such as high dose chemotherapy with autologous bone marrow support, whereas if a broader definition of poor risk defined a group whose overall prospect of survival was more than 70%, then a less hazardous treatment approach would be appropriate. There is broad agreement that the major factors determining prognosis are the extent and bulk of metastatic disease and the concentration of serum alpha-fetoprotein (AFP) and serum human chorionic gonadotropin (hCG) [35, 36]. Some centres have also included serum lactate dehydrogenase [37], and univariate analyses have suggested the relevance of tumour proliferative activity [38, 39].

The Medical Research Council has just completed a prognostic factor analysis on 795 patients treated with chemotherapy for metastatic non-seminoma between 1982 and 1986. The results are in concordance with a similar analysis on separate patients from the EORTC Genitourinary Group. Though many assessments of tumour extent were relevant on univariate analysis, a multivariate analysis suggested that major independent prognostic categories were: (1) presence of 20 or more lung metastases; (2) serum AFP $>$ 1000 iu/l or serum HCG $>$ 10,000 iu/l; (3) mediastinal mass $>$ 5 cm diameter; and (4) liver, bone or brain involvement.

At least one of these factors was present in 169 of the 795 patients and defined a 3 year survival probability of 78% compared with 94% in the 531 patients with none of these features [40].

Chemotherapy for good prognosis non-seminoma

For patients with good prognosis, a number of approaches to reducing chemotherapy toxicity have been explored including reduction or deletion of bleomycin, reduction of the number of chemotherapy cycles and the replacement of cisplatin with carboplatin. A prospective trial has demonstrated that three cycles of BEP are as effective as four [41]. The role of bleomycin (B) remains controversial since a prospective randomised study of EP versus BEP performed by the EORTC has demonstrated no difference in efficacy whereas a recent South Eastern Cooperative Oncology Group Trial comparing only 3 courses of each of these regimens was terminated early because of reduced efficacy of the treatment without bleomyin (L. Einhorn).

The introduction of carboplatin to replace cisplatin in combination schedules for the treatment of germ cell tumours was stimulated by the lack of renal, neural or auditory toxicity of carboplatin. On the other hand, carboplatin appears to have more bone marrow toxicity and dose consideration may be more complex in view of its renal excretion pattern. It has been suggested that the dose of carboplatin be based on an accurate assessment of glomerular filtration rate (GFR) rather than on the patient's size [42]. A pilot study at the Royal Marsden Hospital investigated carboplatin in combination with etoposide and bleomycin (CEB) in germ cell tumours [43]. The conclusion of this study was that carboplatin was safe and effective when administered at a total dose derived from the formula Dose = 5 $\times$ (GFR + 25).

In the Royal Marsden study this was assessed by 51 chromium-EDTA clearance. Of the first 76 patients treated with this combination, the cause-specific survival probability was 98.5%. The single death was due to bleomycin pneumonitis. The 5 patients who relapsed had been treated early in the schedule with relatively low doses of carboplatin emphasising the importance of accurate dose judgement. The current MRC trial in good prognosis patients compares CEB with BEP with bleomycin reduced in both arms in order to avoid the risk of fatal pneumonitis.

Chemotherapy for poor prognosis non-seminoma

For patients in the adverse prognostic group, approaches to increasing the efficacy of chemotherapy have included dose escalation, sometimes supported with bone marrow transplantation, or dose intensification by more frequent drug cycling. Also, the use of alternating schedules has been explored though it is unclear whether the different schedules were truly non-cross resistant. Single centre studies have strongly supported the idea of alternating schedules. These have included the POMB/ACE regimen developed at the Charing Cross Hospital, London [44] and the CISCA/VB schedule developed at the M. D. Anderson Hospital [45]. However, a prospective randomised trial of alternating PVB/BEP did not produce better results than pure BEP [46].

High dose carboplatin and etoposide with autologous marrow support has been explored mainly in the context of relapsed and refractory germ cell tumours. This is an extremely poor prognostic group and merits an aggressive approach to treatment. The extent of previous treatment led to severe problems of bone marrow toxicity and of the first 33 patients entered into this study, there were 7 treatment deaths associated with granulocytopenia and infection. Of 7 complete remissions 4 were clearly in patients refractory to standard doses of cisplatin [47].

A different approach to intensification of treatment has been to reduce the interval between courses of chemotherapy. A number of single arm studies have explored this method of intensifying chemotherapy in high risk cases [48–50]. Due to differences in patient entry criteria and time of analysis, it remains unclear whether treatment intensification has any impact on the survival of patients with adverse prognosis. It has been demonstrated by prospective randomised trial that the combination of bleomycin, etoposide and cisplatin is superior to cisplatin, vinblastine and bleomycin [51]. It is therefore appropriate to use the BEP schedule as the standard control arm in prospective evaluation of the more intensive chemotherapy regimens. The Medical Research Council and EORTC Genito-urinary Group are jointly performing a prospective randomised trial of BEP versus BOP/VIP. BOP/VIP consists of an intensive bleomycin, vincristine and cisplatin induction phase with chemotherapy cycles every 10 days followed by a conventional cycling of etoposide, ifosphamide and cisplatin. It certainly cannot be assumed that more intensive treatment will improve response or cure rates compared with standard BEP.

A prospective randomised trial by the SECSG compared BEP with the cisplatin dose at 100 mg/m^2 with the same schedule with cisplatin at 200 mg/m^2. With 141 evaluable patients, there was no significant difference between the two treatment regimens in complete remission rate, relapse rate or survival [41]. This would argue that a doubling of dose intensity would not in itself be enough to overcome resistance mechanisms in advanced non-seminoma.

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Neoadjuvant and Adjuvant Therapy for Invasive Bladder Tumours

Luc Y. Dirix and Allan T. Van Oosterom

INTRODUCTION

ALTHOUGH BLADDER cancer is the fifth most common cancer in the Western world, it is only seventh in the ranking of cancer related mortality. This is due to its presentation as a superficial disease in 80–90% of new cases. Only 10% and 30%, respectively, of Tis and T1 cancers will actually develop into invasive carcinomas. The majority of patients who will eventually die of bladder cancer have muscle invasive disease at presentation. A clear distinction must therefore be made between muscle invasive and non-invasive disease, as those two entities have completely different biological behaviour, and as progression from non-invasive to invasive disease only occurs in a minority of patients [1].

The prognostic importance of muscle invasive disease is its metastatic potential [2]. At present we are hampered by the lack of reliable prognostic factors that would enable us to distinguish between local invasiveness of a tumour and its metastasing capacity. The entire group of patients with a muscle-invasive tumour has a 5-year survival rate of less than 50% regardless of the local treatment strategy applied [3]. The majority of those patients will succumb due to metastases making T2+ bladder cancer a systemic disease.

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