MANAGEMENT OF TESTICULAR CANCER

Peter S Grimison[1] and Guy C Toner[2]
1. Sydney Cancer Centre, Royal Prince Alfred Hospital, Sydney, NSW and University of Sydney, NSW.
2. Peter MacCallum Cancer Institute, Victoria and University of Melbourne, Victoria.
Email: Peter.Grimison@sswahs.nsw.gov.au

Abstract

The management of testicular cancer has changed dramatically over the last 30 years. Almost all patients with early stage disease and over 80% of patients with advanced disease can now be cured with optimal treatment in experienced cancer centres. Strategies for stage I seminoma are surveillance, adjuvant radiotherapy or adjuvant chemotherapy with carboplatin. Strategies for stage I non-seminoma are surveillance or two cycles of adjuvant combination chemotherapy. First-line treatment for advanced disease is combination chemotherapy. Salvage treatment for early relapse of advanced disease is standard or high-dose chemotherapy. Current controversies for stage I disease include the appropriate selection of patients with stage I disease for surveillance or adjuvant therapy, the optimal surveillance program and the nature and intensity of adjuvant therapy. Current controversies for advanced disease include the role and timing of high-dose chemotherapy. Priorities for future research are identified.

The majority of testicular neoplasms are germ cell tumours, which arise from the malignant transformation of primordial germ cells that are destined to become spermatids. Testicular germ cell tumours are classified for treatment purposes into two subtypes. About 50% are pure seminoma and are highly sensitive to radiotherapy and chemotherapy. The remainder are grouped as non-seminomatous germ cell tumours (non-seminoma) and include yolk sac tumour, embryonal carcinoma, choriocarcinoma, teratoma with mature or immature elements, and tumours with a mixture of these elements. Tumours with any non-seminomatous component or an elevated alpha-fetoprotein (AFP) are treated as non-seminoma.[1] Mature teratoma is a slow growing chemo resistant tumour that can occasionally undergo malignant transformation to adenocarcinoma or sarcoma if left unresected.

About 80% of patients with seminoma and 60% of patients with non-seminoma have disease restricted to the testis (stage I) at diagnosis. Current research for this group aims to reduce the toxicity of treatment while maintaining high cure rates. Advanced disease includes metastases to infra-diaphragmatic lymph nodes (stage II) and distant metastases (stage III). Serum tumour markers including AFP, human chorionic gonadotrophin (HCG) and lactate dehydrogenase (LDH) play a vital role in diagnosis, prognostication, assessment of response and monitoring for relapse and have recently been incorporated into the TNM staging system.

All patients with testicular cancer should be treated with curative intent, regardless of stage of disease. Best outcomes occur in high volume, specialised treatment centres that use an integrated multidisciplinary approach.[2] Expertise is required in the fields of oncology (urological, medical, radiation), nursing, psychology and andrology. Infertility may occur due to treatment, or even before treatment, so patients should be offered sperm-banking prior to chemotherapy or radiotherapy.

Management of stage I seminoma

At least 80% of patients with stage I seminoma are cured with orchidectomy alone. Of the 15-20% who relapse after orchidectomy, almost all recur initially in infra-diaphragmatic lymph nodes with a predictable pattern of spread. About two thirds of patients who relapse will do so in the first two years, but there is a small risk of relapse extending until 12 years following orchidectomy.[3] The presence of tumour invasion into the rete testis and tumour size greater than 4cm increases the risk of relapse to 31%, but absence of both factors reduces the risk to 12%. Unlike stage I non-seminoma, lymphovascular invasion is not an independent risk factor for relapse.[4]

The appropriate management strategy for stage I seminoma remains controversial. Until recently, almost all patients with seminoma received adjuvant radiotherapy.[5] Traditionally, adjuvant radiotherapy to a dog-leg field (para-aortic and ipsilateral pelvic lymph nodes) was used, reducing the risk of relapse to 5% or less. Potential long-term toxicities include chronic gastrointestinal side-effects, cardiovascular disease, infertility (for pelvic radiotherapy) and radiation induced second malignancies.[3] The small risk of developing a second malignancy has been a major concern with this approach. The Medical Research Council UK has conducted two randomised trials which aimed to reduce long-term toxicity. Treatment with lower doses (20 Gy versus 30 Gy)[6] and smaller fields (para-aortic region versus dog-leg field),[7] were associated with equivalent relapse free survival. Long-term follow-up of these trials is required to determine if less intense radiotherapy achieves the goal of reducing long-term toxicity.

Surveillance for seminoma was introduced by selected centres during the 1980s as an alternative to adjuvant radiation therapy.[4] The main disadvantage of surveillance is the need to follow patients intensively for at least 10 years. Follow-up requires clinical examination, tumour markers and repeated CT scans of the abdomen and pelvis. Poor compliance with surveillance increases the

likelihood of presenting at relapse with bulky disease that requires intensive multimodality therapy.[3] The optimal surveillance protocol has not been defined and published guidelines vary widely. Minimum recommendations are: six to eight visits and four to eight CT scans during the first two years; six to 10 visits and three to eight CT scans during the next three years; then annual visits with zero or one annual CT scan up to 10 years.[8-10] Repeated CT scans may be also associated with a small increased risk of radiation induced malignancies.[11] A current randomised trial conducted by the Medical Research Council is testing if excellent outcomes can be maintained when reducing radiation exposure by substituting MRI for CT and/or reducing the number of scans.

Adjuvant chemotherapy with a single dose of carboplatin has been compared to adjuvant radiotherapy in a recent randomised clinical trial conducted by the Medical Research Council and the European Organisation for Research and Treatment of Cancer.[12-13] Relapse rates were similar for carboplatin compared with radiotherapy, but did not meet the definition of non-inferiority stipulated in the protocol. The pattern of relapse varied - patients treated with carboplatin were more likely to relapse in lymph nodes below the diaphragm, while patients treated with radiotherapy were more likely to relapse above the diaphragm (outside the treatment field). Most acute toxicities were better for patients receiving carboplatin. Patients treated with carboplatin were less likely to develop contralateral germ cell tumours. Carboplatin has not yet been fully accepted as a standard management strategy.[3] Long-term data about relapse and survival is awaited. The optimal number of cycles of carboplatin is not defined.[14-15] Carboplatin is expected to have little late toxicity but longer term follow-up data is required. The incidence of cardiovascular disease and second malignancies do not appear to be increased at a median of nine years of follow-up.[16] It is important to note that patients receiving carboplatin require ongoing follow-up including repeated abdominal and pelvic CT scans.

As a result of the effectiveness of treatment for relapsed disease, all management strategies including surveillance give 97-100% cancer-specific survival in experienced centres.[3] The selected strategy should be tailored to the risk of relapse, patient preference and local expertise and familiarity with the chosen strategy.

Management of stage I non-seminoma

Seventy to 75% of patients with stage I non-seminoma are cured with orchidectomy alone. Of the 25 to 30% who relapse, 60% recur initially in retro-peritoneal lymph nodes and almost all of the remainder in the lungs. A series of studies has shown that about 80% of patients who relapse will do so within one year, 10% during the second year and 5% during the third year. Relapse beyond five years is rare.[8] The strongest risk factor for relapse is vascular invasion of tumour into blood or lymphatic vessels. Other weaker risk factors are high tumour proliferation rate, presence of embryonal cell carcinoma and absence of yolk sac elements. High and low risk patients have a risk of relapse at three years of 35-40% and 10-15% respectively.[17]

Patients with stage I non-seminoma can be managed with surveillance or adjuvant chemotherapy. Each management strategy should give 98-99% cancer specific survival in experienced cancer centres.[1,3]

Patients on a surveillance program require strict follow-up, because delayed detection of relapse in patients with inadequate surveillance may result in bulkier disease at relapse with poorer outcomes. Recommendations vary substantially on the minimum surveillance requirements for stage I non-seminoma: eight to 18 visits and two to seven CT scans during the first two years; six to 10 visits and zero to six CT scans during the next three years; then zero or one annual visit and zero or one annual CT scan up to 10 years.[8-10] The substantial variation in recommendations has led to uncertainty by clinicians about appropriate follow-up schedules.[18] The Medical Research Council recently conducted a randomised trial that compared surveillance with two CT scans during the first 12 months, with five CT scans over 24 months.[19] A similar proportion of patients in each arm relapsed with intermediate or poor-risk metastatic disease at a median of 40 months. The applicability of this trial is limited by the low proportion of patients with high risk disease (10%), the lack of long-term follow-up data on outcomes after relapse and questionable choice of the control arm and the primary measure of effectiveness.

Adjuvant chemotherapy for stage I non-seminoma generally consists of two cycles of chemotherapy with cisplatin, etoposide and bleomycin (BEP). This treatment reduces the risk of relapse to about 2%.[3] Two cycles of BEP does not appear to adversely affect fertility or sexual function.[20]

Disadvantages of adjuvant chemotherapy are over-treatment in those who will remain relapse free without adjuvant therapy - about 90% of low risk patients and about 60% of high risk patients. These patients are at risk of unnecessary long-term toxicity including neuropathy, Raynaud's disease, cardiovascular disease, and rarely secondary haematological malignancies.[3] Another concern is the potential for late relapse in infradiaphragmatic lymph nodes of slow growing chemo-resistant teratoma. This mandates ongoing and long-term follow-up.[21] The Swedish-Norwegian Testicular Cancer Project recently conducted a study using only one cycle of BEP for high risk non-seminoma (and surveillance for low risk non-seminoma).[22] The relapse rate of 3% at a median of almost five years is comparable to two cycles of BEP. Mature data is awaited from this study, however the applicability will remain limited by the sample size and methodology and two cycles of BEP will likely remain the standard for adjuvant chemotherapy.

Retroperitoneal lymph node dissection with or without adjuvant chemotherapy is a third option that is not commonly practised in Australia because of concerns about its acute and chronic complications, including bowel dysfunction and reterograde ejaculation, and because of the excellent results with alternative strategies.[9-10]

Guidelines recommend risk adapted treatment for the majority of patients. Surveillance is generally preferred for compliant patients with low risk disease (as defined

by lack of vascular invasion). Adjuvant chemotherapy is generally preferred for high risk disease, but surveillance remains an option. As for seminoma, treatment should be customised for each patient according to risk of relapse, patient preference and the expertise of the treating team.

Initial management of advanced disease

The majority of patients with advanced disease can still be cured with modern platinum based chemotherapy, however 25% will relapse and 20% will eventually die of their disease.[23] The International Germ Cell Cancer Collaborative Group (IGCCCG) have identified adverse risk factors that predict poorer outcomes: presence of a mediastinal primary site; degree of elevation of tumour markers (AFP, B-HCG, LDH) and; presence of non-pulmonary visceral metastases (ie. not lymph node or lung; eg. liver, brain or bone metastases). The 60% of patients classified with a good prognosis by IGCCCG criteria have a five year survival of 90%. The 25% of patients with intermediate risk disease and 15% of patients with poor risk disease have a five year survival of 80% and 50% respectively.[23] Since publication of this data there has been an increasing proportion of patients in the good prognosis category and outcomes for those in the intermediate and poor prognosis groups have improved.

Non-bulky metastatic pure seminoma involving only infra-diaphragmatic lymph nodes (stage IIA) is usually treated with external-beam radiotherapy. 'Non-bulky' is generally considered to be when the maximum diameter of the nodal disease is <5cm. Some centres use a 3cm cut-off. Relapse occurs in about 10% of patients, with overall survival approaching 100%.[1] Four cycles of single-agent carboplatin appears to be inferior to radiotherapy in stage II seminoma.[24]

Standard initial treatment for all other patients with advanced disease (regardless of risk group) is BEP chemotherapy.[25] Patients with good risk disease receive three cycles of BEP and patients with intermediate or poor risk disease receive four cycles of BEP.[26] Potential long-term toxicity of chemotherapy includes infertility, ototoxicity, Raynaud's phenomenon, peripheral neuropathy, lung disease, cardiovascular disease and secondary malignancies.[26]

A randomised trial conducted by the Australia New Zealand Germ Cell Trials Group (now incorporated in the Australian and New Zealand Urogenital and Prostate Cancer Trials Group Ltd [ANZUP]), has shown that the dose and dose intensity of BEP is important.[27] For good risk disease, a randomised trial conducted by the French Federation of Cancer Centres suggests that four cycles of etoposide and cisplatin (EP) is equivalent to three cycles of BEP.[28] Advocates of BEP favour the shorter duration of treatment and greater evidence base for this approach, while advocates of EP favour the omission of bleomycin with reduction in interstitial lung disease and Raynaud's phenomenon. For intermediate and poor risk disease, randomised trials of more toxic regimens, including VIP (etoposide, ifosfamide, cisplatin)[29-30] and high dose chemotherapy with stem cell support,[31] have been shown to be more toxic than BEP, but no more effective. Alternate regimens that are currently being evaluated in the first line setting include paclitaxel in combination with BEP (T-BEP) and a multi-drug, dose dense regimen of carboplatin, bleomycin, vincristine, cisplatin and BEP. ANZUP is completing a trial of accelerated BEP, cycling cisplatin and etoposide every two weeks instead of every three weeks. ANZUP is advancing a proposal for an international randomised trial to compare accelerated BEP with standard BEP. Current research is also testing intensification of chemotherapy for patients with inadequate fall of tumour markers during BEP chemotherapy.

A key component of the management of advanced non-seminoma is resection of residual masses after chemotherapy.[26] In patients with normalisation of tumour markers, resection of residual masses yields viable germ cell tumour in 10%, mature teratoma in 50% and necrosis in 40%. In contrast, resection of residual masses for pure seminoma is not recommended because the low incidence of viable tumour or chemo-resistant teratoma, and because surgery is technically difficult because chemotherapy induces an intense fibrotic reaction.[26] For seminoma, PET scans can be used to determine the presence of viable tumour that requires further treatment.[32]

Salvage treatment for relapsed disease

Patients refractory to or relapsing after initial treatment for advanced disease can still be cured with salvage treatment. A recent report identified adverse prognostic factors for response to salvage treatment as non-gonadal primary site, absence of complete response to initial chemotherapy, progression free interval of less than three months, degree of elevation of tumour markers at relapse, and the presence of non-pulmonary visceral metastases at salvage.[33] Patients with low risk, intermediate risk and high risk disease have a three year survival of 73%, 59% and 27% respectively. The majority of patients fall into the intermediate group.

Standard approaches for patients who relapse within two years from initial treatment (early relapse) are four cycles of conventional dose chemotherapy (usually paclitaxel, ifosfamide and cisplatin [TIP]), or two to three cycles of sequential high-dose chemotherapy with peripheral blood stem cell support (eg. two cycles of paclitaxel and ifosfamide followed by three cycles of high dose carboplatin and etoposide [TICE]).[26] It is not yet clear if patients should receive high dose chemotherapy as first line salvage treatment for poor prognosis relapse, or if it should be reserved as second line salvage treatment. Patients who relapse more than two years after first line chemotherapy (late relapse) appear to have more chemo resistant disease in which surgical resection of all metastatic tumour may play an important role in management.[21]

Research priorities

Research priorities in the management of stage I testicular cancer are to maintain high cure rates while reducing the potential long-tem toxicity of adjuvant treatment and surveillance CT scans. An important strategy is to identify genetic and molecular predictors of relapse that will better select patients who will benefit from adjuvant therapy and

avoid over-treatment in other patients. Another strategy is the investigation of utility of new imaging modalities such as PET-CT scans to detect occult metastatic disease.

For advanced testicular cancer, more effective regimens are required for patients with intermediate and poor risk disease. One strategy aims to identify pharmacogenetic markers of bleomycin and etoposide metabolism, with use of alternate chemotherapy regimens in patients with high clearance. Another strategy aims to identify molecular predictors of incomplete response or relapse, which will select patients for more aggressive first line chemotherapy.

Most patients treated for testicular cancer will be cured and live for many decades. It is only about 30 years since the introduction of effective chemotherapy and, as a result, we are still learning about the late effects of treatment. Understanding the outcomes in survivors remains an important area of research.

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