Adjuvant chemotherapy for stage I non-seminomatous testicular cancer

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Developments in the treatment of stage I testicular non-seminomatous germ cell tumours have aimed primarily at reducing morbidity since the introduction of retroperitoneal lymph node dissection. Surveillance after orchidectomy, i.e. follow-up alone with chemotherapy only for relapsed disease, was found to be logistically and psychologically taxing for patients. Risk factors for relapse were, however, identified from analyses of tumour histology of the orchidectomy specimen.

Between September 1988 and April 1992, 20 patients with clinical stage I testicular non-seminomatous germ cell tumours and a relatively high risk of relapse were entered into a prospective study of adjuvant chemotherapy. The chemotherapy regimen consisted of 2 cycles of cisplatin, etoposide and bleomycin. Each cycle of chemotherapy lasted 3 days.

There have been no relapses at a median follow-up of 31 months (range 12 - 53 months). Acute and late toxicity have been modest. We have found adjuvant chemotherapy to be effective after orchidectomy in patients with stage I disease with adverse prognostic factors for relapse.

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Testicular tumours constitute 1 - 2% of all malignancies in men and are the most common malignancy in the economically active age group of 15 - 35 years.[1] They are divided approximately equally into seminomas and non-seminomatous germ cell tumours (NSGCTs). Seminomas are radiosensitive and patients with stage I disease (clinically localised to the testis) have been treated since the 1920s with retroperitoneal irradiation.[2,3] Patients with stage I NSGCT have undergone retroperitoneal lymph node dissection (RPLND) in many centres since the 1960s.[4] The aim of RPLND is to stage patients accurately; it is also curative in a proportion of patients with lymph node metastases.

The introduction of cisplatin combination chemotherapy in the 1970s resulted in cures in the majority of patients with metastatic NSGCT.[5,6] This led to a re-evaluation of the need

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for RPLND in patients with stage I NSGCT. Surveillance studies were undertaken with follow-up only after orchidectomy and chemotherapy for patients with relapsed disease.[7] This approach resulted in cure rates of close to 100%, but was found to be logistically and psychologically taxing for patients.[8]

Analysis of tumour histology in the orchidectomy specimen in patients entered into surveillance studies led to the identification of risk factors for relapse.[9] A prospective study of adjuvant chemotherapy was undertaken in patients with stage I testicular cancer with a relatively high risk of relapse. The chemotherapy regimen used had been designed to minimise toxicity.[8]

Materials and methods

Twenty patients with clinical stage I NSGCT were treated with adjuvant chemotherapy between September 1988 and April 1992 at Groote Schuur Hospital, Cape Town, Provincial Hospital, Port Elizabeth and Frere Hospital, East London. The patients had all undergone an orchidectomy and staging investigation included negative serum tumour markers (α-fetoprotein and β-human choriogonadotrophin), chest radiographs and computed tomography (CT) of the abdomen. The median patient age was 25 years (range 20 - 35 years).

Adverse prognostic factors for relapse are determined from the histological features of the orchidectomy specimen according to the findings of the British Medical Research Council. These were the presence of undifferentiated carcinoma (embryonal carcinoma), the absence of yolk sac tumour and the presence of vascular or lymphatic invasion. There were 2 adverse prognostic factors present in 2 patients and either 3 or 4 such factors in the remainder.

Adjuvant chemotherapy consisted of 2 cycles of combination chemotherapy given 3 weeks apart. Each cycle consisted of 3 daily injections of cisplatin (35 mg/m^2), etoposide (120 mg/m^2) and bleomycin (15 mg over 7 hours). Patients were hydrated with a minimum of 3 litres of fluid per day.

Results

There were no relapses at a minimum follow-up of 12 months in all patients. The median length of follow-up was 31 months (range 12 - 53 months).

Toxicity was minimal with no acute grade 3 or grade 4 leucopenia or thrombocytopenia. There have been no acute or late episodes of renal or pulmonary toxicity.

Discussion

Developments in the treatment of stage I NSGCT since the introduction of RPLND have aimed primarily at reducing morbidity. RPLND may result in failure of semen emission (ejaculatory impotence) because of dissection of the sympathetic nerves overlying the major vessels.

The introduction of effective chemotherapy for NSGCT resulted in MRC surveillance studies of patients with stage I NSGCT. The 4-year relapse rate was 32% and virtually all relapsing patients were saved with chemotherapy.[7] However, surveillance was found to be logistically demanding, and required multiple follow-up evaluations, including abdominal CT; it was also stressful to patients afraid of possible relapse.[8] Some patients even reported relief at the diagnosis of metastatic disease as they could now receive definitive therapy.

Review of the histology of the orchidectomy specimen allowed for the identification of adverse prognostic factors for relapse. The 2-year relapse-free rate for patients with 0, 1, 2 and 3/4 adverse prognostic factors present was 100%, 91%, 75% and 52% respectively.[9] The proportion of all cases according to the relapse factors above were 3%, 31%, 34% and 42%. Patients with a high risk of relapse, especially those with 3 or 4 adverse factors, are particularly suitable candidates for adjuvant chemotherapy. Patients with 2 adverse factors may choose to have adjuvant therapy even though their chance of relapse is lower.

Adjuvant chemotherapy has been found to be effective in patients with stage II disease undergoing RPLND.[10] In a prospective trial of 195 patients, the relapse rate for patients treated with RPLND alone was 49% and that for patients receiving 2 cycles of chemotherapy was 0%. The toxicity was also relatively low. It is noteworthy that toxicity from 4 cycles of chemotherapy is worse than from 2 cycles of chemotherapy.[8]

The chemotherapy used has a relatively low toxicity. The duration of hospitalisation per cycle of chemotherapy is reduced from 5 to 3 days and the use of bleomycin by infusion over 3 days may be associated with reduced pulmonary toxicity.

The MRC study of adjuvant therapy used 2 cycles of 5-day cisplatin combination chemotherapy. There is one report of adjuvant therapy for testicular cancer where 3 cycles of the more toxic PVB regimen[11] (cisplatin, vinblastine and bleomycin) are given. No relapses were seen in 30 patients at a median follow-up of 31 months (range 14 – 60+ months).[12]

We have found adjuvant chemotherapy after orchidectomy effective in patients with stage I disease and adverse prognostic factors for relapse. Further follow-up is being undertaken. Adjuvant chemotherapy is well tolerated and associated with minimal morbidity. Should similar findings emerge from the British MRC and other studies, we believe that it will become the treatment of choice in these patients.

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