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Letters

Low-dose Fortnightly Methotrexate in Advanced Prostate Cancer

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THE Genito-Urinary Tract Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) has performed a series of phase II studies with strict criteria for the assessment of response in patients with bidimensionally measurable soft tissue or visceral metastases [1, 2]. Reviewing chemotherapy in urological tumours, Stoter and Williams [3] concluded that methotrexate was not useful in the treatment of prostate cancer. Response to methotrexate in the American National Prostatic Cancer Project (NPCP) protocol 1100 was only 5% [4]. However, the scheduling of methotrexate doses was under investigation in the mid-1980s and in view of activity in other adenocarcinomas (e.g. breast cancer), together with anecdotal reports of activity in prostate cancer, a phase II study of 'low-dose' methotrexate (40 mg/m^2) given every 2 weeks was started to investigate the effectiveness and toxicity of this schedule in prostate cancer patients.

Entry criteria included: positive histology, bidimensionally measurable (clinical, ultrasound, computed tomography) soft tissue or visceral lesions to assess response, age 75 or less, additive hormone therapy to be stopped at least 1 day before the start of therapy, no previous chemotherapy or radiotherapy to the indicator lesion(s), WHO performance status 2 or better, life expectancy greater than 60 days, initial white blood count 3×10^9/l or greater, initial platelet count 100×10^9/l or greater, adequate renal function (serum creatinine 120 μmol/l or less, creatinine clearance greater than 75 ml/min), adequate liver function (bilirubin less than 20 mmol/l), no second tumour, no significant cardiac disease, and no uncontrolled infections. Response was assessed after every two cycles. WHO criteria for evaluation of response and toxicity were used [5].

28 patients with documented progressive hormone-resistant disease entered the study between January 1986 and April 1989. 4 patients were ineligible; 1 had no measurable lesion and 3 had not received previous hormone therapy as required by the protocol. Of the 24 eligible patients (age 46–75 years, median 63.5 years), all had received previous androgen suppressive therapy; in addition 2 had received estramustine phosphate and eight had received radiotherapy to various sites. WHO performance scores were: 0 in 4 patients, 1 in 14, and 2 in 6.

1 patient died before the first assessment after two cycles (early death from malignant disease). 1 patient died of toxicity after one cycle (early death from toxicity) with nausea and vomiting WHO grade 3, diarrhoea grade 4, oral toxicity grade 4, liver toxicity grade 1, renal toxicity grade 1 and minor haemorrhage. A toxic death was also reported in 1 patient who had a further cycle of therapy after withdrawing because of progression.

No complete responses were observed. One patient (5%) had a partial response in inguinal lymph nodes, 10 patients (46%) showed no change and 11 patients (50%) had progressive disease.

Full doses of drug were given with all cycles of treatment. Leucovorin rescue was only given if toxicity was encountered. The median number of courses was two (mean 3.5, range 1–10). The dose was delayed (3–7 days) on three occasions.

Haematological toxicity was tolerable. The lowest white cell count was 3.2×10^9/l (range $3.2–9.7 \times 10^9$/l, median 4.5×10^9). The lowest platelet count was 17×10^9/l (range $17–530 \times 10^9$/l, median 174×10^9).

Methotrexate at a dose of 40 mg/m^2 given every 2 weeks (with or without leucovorin rescue) was inactive in hormone resistant metastatic prostate cancer. Our results were similar to those reported from the NPCP protocol 1500 [6]. The therapy has considerable toxicity and toxic deaths occurred. Thus methotrexate has no place in the treatment of this disease.

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