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Single Agent Activity of Methotrexate in Advanced Non-seminomatous Testicular Germ Cell Tumours

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Abstract—*The single agent activity of methotrexate in non-seminomatous germ cell tumours (NSGCT), and thus the rationale for its inclusion in combination regimens, has never been documented clearly. We have therefore reviewed all patients with NSGCT treated in this hospital from* 1967 *to* 1970. *Seventeen patients were identified who had a rising HCG excretion and who were treated with methotrexate alone as first line chemotherapy.*

Nine patients (53%) *obtained a partial remission and a further seven patients a reduction in HCG production that was less than one log. Methotrexate is an active agent in testicular germ cell tumours and should be of particular value in treating CNS disease where intrathecal treatment may be required.*

INTRODUCTION

METHOTREXATE has been one of the most useful drugs in the curative management of trophoblastic disease in women for more than 30 years [1]. Approximately 50% of patients with metastatic NSGCT have an elevated serum human chorionic gonadotrophin (HCG) presumably produced by trophoblastic elements which might be expected to respond to methotrexate [2]. Despite this there are little published data on the activity of methotrexate in testicular tumours and with the success of combination chemotherapy new prospective single agent data in untreated patients will not be available. In this paper we report the single agent response rate of methotrexate in a group of patients treated in this hospital between 1967 and 1970.

PATIENTS AND METHODS

The records of all patients with non-seminomatous testicular germ cell tumours treated between 1967 and 1970 in the Department of Medical Oncology, Charing Cross Hospital, London, were reviewed. Those patients who had received methotrexate as first line single agent therapy for metastatic disease and who had urinary HCG measured prior to the start of therapy were considered eligible for study. Methotrexate was administered either by daily i.v. injections of 25 mg for 7 days or as four i.m. injections of 50 mg alternating with four i.m. doses of folinic acid 6 mg 30 h after each dose of methotrexate. Courses were repeated following a 5–10 day drug free interval depending on haematological recovery.

HCG was measured in the urine by radio-immunoassay as previously described [3]. Values reported are for 24 h excretion.

Response to treatment was assessed by monitoring HCG excretion. A partial remission was defined as a greater than one log fall in 24 h HCG excretion maintained for at least 4 weeks. Remissions were confirmed by review of the relevant radiological data.

RESULTS

Seventeen patients were identified who had received single agent methotrexate as first line chemotherapy for advanced NSGCT and in whom the HCG excretion was rising prior to the start of treatment. All patients had stage IV bulky disease (>5 cm nodal or >2 cm lung metastases) according to the Royal Marsden staging system [4]. In 16 patients the lungs were the major site of disease and in one the para-aortic lymph nodes. Patient characteristics are summarized in Tables 1 and 2.

Nine of these 17 patients, 53% (95% confidence intervals 28–77%), achieved a marker partial remission. In five cases this occurred after only one

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Table 1. Patient characteristics

Total number of patients	17
Age median (range)	30 (18–40)
Prior radiotherapy	6
Disease sites: lungs	16
para-aortic nodes	9
SCF nodes	6
CNS	2
axillary nodes	1
liver	1
Stage IV disease	17

cycle of methotrexate and in the remaining four after two cycles. A typical HCG chart for one patient is shown in Fig. 1. Remissions were maintained for a median of 45 days (range 31–75 days). Review of X-rays confirmed the correlation of marker remission with objective partial response.

Of the eight patients not achieving a marker remission, seven showed a less than one log fall in HCG excretion and in only one was there a progressive rise through methotrexate therapy.

Patients received a median of three cycles of methotrexate (range 1–5) and on progression were treated with a variety of single agents including Actinomycin-D, chlorambucil, vinblastine and cyclophosphamide. Median survival from the start of methotrexate therapy was 180 days (range 53–1064).

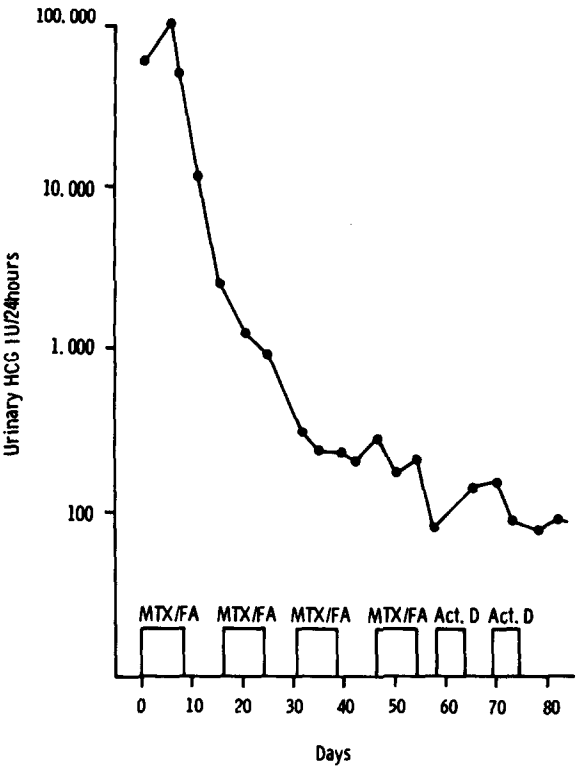

Fig. 1. The fall in urinary HCG excretion during treatment in one patient.

DISCUSSION

This study clearly demonstrates that methotrexate is an effective single agent in patients with NSGCT. Nine of 17 patients (53%) achieved a partial remission and in only one case was there clear evidence of progression during therapy. These results are similar to those of Wyatt and McAninch [5] who obtained responses in four of 10 patients with NSGCT. All four responders became long term survivors as did two patients also treated with methotrexate alone from a review of 18 reports by Smithers [6]. Methotrexate thus appears to have a response rate of the order of 40–50% in NSGCT and in some cases can produce durable remissions. This response rate compares favourably with the most active drugs in this disease [7–10] although

Table 2. HCG response and survival

Patient	No. of cycles	HCG iu/24 h Pre Mtx	HCG iu/24 h Post Mtx	Duration of response (days)	Survival (days)
IB	3	1.6×10^5	1.6×10^4	41	145
AB	2	6.8×10^5	2.2×10^4	42	179
RB	5	2.0×10^5	4.0×10^2	75	513
CF	4	2.0×10^6	2.0×10^4	53	148
RH	4	1.0×10^5	6.6×10^2	42	491
GMc	3	2.6×10^5	3.6×10^3	45	202
JS	4	6.0×10^4	7.8×10^1	58	1064
ET	2	2.7×10^4	2.7×10^3	31	245
PD	3	1.3×10^6	1.4×10^4	45	175
TG	2	1.1×10^4	9.0×10^3	—	88
JH	1	1.6×10^5	3.2×10^4	—	180
AS	2	6.0×10^4	3.5×10^4	—	182
DT	3	6.4×10^5	9.0×10^4	—	456
RW	2	8.5×10^4	2.0×10^4	—	116
JS	1	9.5×10^4	5.4×10^4	—	218
BL	3	1.5×10^6	2.0×10^5	—	113
DP	2	3.0×10^5	3.5×10^6	—	53

there is evidence that it is inactive in patients resistant to cisplatin [11]. Moreover, the activity demonstrated in the present study applies only to patients whose tumours contain trophoblastic elements. However, it has been shown that patients with serum HCG levels >50,000 iu/l have a particularly poor prognosis [12] and in addition most cerebral metastases from NSGCT occur in patients with high serum HCG levels [13]. Methotrexate which can be administered both systemically and intrathecally would therefore appear to be part of the optimum management of these groups of patients. Moreover, the use of folinic acid rescue allows methotrexate to be used with minimal toxicity and it is therefore particularly valuable for inclusion in high dose intensity combination regimens where myelosuppression is often a limiting factor.

This study also demonstrates the validity of the use of tumour markers in monitoring the response to therapy with a greater than one log fall in urinary HCG correlating closely with a 50% reduction in evaluable disease. Indeed HCG and AFP often provide a more accurate assessment of response in NSGCT since cystic differentiated teratoma may increase in size during therapy giving a false impression of tumour progression.

In conclusion methotrexate has single agent activity of the order of 40–50% in NSGCT and appears to be of particular value in tumours containing trophoblastic elements. Moreover, since patients with high HCG levels have been identified as a poor prognostic group [12] methotrexate should be part of their optimum management. In addition the close correlation between tumour marker response and objective tumour regression has been demonstrated.

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