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Single Agent Etoposide in Gestational Trophoblastic Tumours

Experience at Charing Cross Hospital 1978–1987

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Abstract—*Two hundred and two patients with gestational trophoblastic tumours (GTT) were treated using single agent etoposide. Patients were divided into low, medium and high risk groups using a prognostic index. Initial chemotherapy commenced with etoposide in* 101 *patients and* 94 *were assessable. Partial response (PR), defined by a log fall in serum human chorionic gonadotrophin (hCG) concentration within* 1 *week, occurred in* 63 *patients* (67%) *and was more common among low* (5/8; 63%) *and medium risk* (47/64; 73%) *than high risk patients* (11/22; 50%) *although these differences were not significant* ($P > 0.05$). *No patient showed a sustained rise in hCG level after etoposide and* 91 (97%) *showed some decrease. Ninety-one* (97%) *of these patients remain alive and well with median follow-up of* 63 *months but* 29 (31%) *required more intensive combination therapy. Of three deaths, two were due to progressive disease and drug resistance.*

Among 101 *patients who had received previous chemotherapy when etoposide was first administered, response to etoposide was assessable in* 39. *Of these, PR occurred in* 18 (46%) *and only one patient progressed after etoposide. With a median follow-up of* 35 *months, survival in this group is* 92% (36/39). *All deaths were due to progressive disease and drug resistance.*

Single agent etoposide is very active in GTT but should be used in combination chemotherapy for patients presenting with adverse prognostic factors.

INTRODUCTION

Cytotoxic chemotherapy is very effective in gestational trophoblastic tumours (GTT) and cure rates in excess of 90% overall can be achieved with currently available protocols [1–5]. Major causes of treatment failure are early deaths from extreme tumour bulk in the lungs and from intracranial metastases, or the late development of drug resistance [4, 5].

Methotrexate (MTX) has been the mainstay of therapy for 30 years for patients with good prognosis disease. However, 25% of such patients ultimately require other drugs due to development of MTX resistance (19.6%), or because of unacceptable side-effects [5]. Patients with poor prognosis disease develop MTX resistance even more readily (69%) and their initial therapy should be more aggressive [5]. At this institution since 1973, patients have been divided into low, medium and high risk groups by prognostic index (Table 1) and initial therapy adjusted accordingly [6, 7]. Low risk patients received single agent MTX. Medium risk patients received sequential treatment with a number of agents and this strategy allowed assessment of new cytotoxic drugs at the start of therapy. High risk patients received intensive combination chemotherapy.

Etoposide (VP16-213, VEPESID, Bristol-Myers) activity in GTT was demonstrated in 1977 based on small numbers of patients [8, 9] and the drug was incorporated into our protocols for medium and high risk groups [4, 5, 10]. Since then, sequential chemotherapy involving single agent etoposide followed by hydroxyurea, MTX, 6-mercaptopurine, cyclophosphamide (CTX), vincristine (VCR) and actinomyin D (ACT-D) has resulted in 100% long term survival among medium risk patients while combination chemotherapy using the EMA/CO regimen (etoposide, MTX and ACT-D alternating weekly with CTX and VCR) in high risk patients has produced 84% long term survival [4, 5].

Despite its apparent contribution to cure in poor prognosis GTT, the single agent activity of etopo-

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Table 1. Prognostic scoring system for gestational trophoblastic tumours

	0	1	2	6
Age (years)	<39	>39		
Antecedent pregnancy (AP)	Mole	Abortion or unknown	Term delivery	
Interval from AP (months)	<4	4–7	7–12	>12
HCG (IU/l)	10^3–10^4	$<10^3$	10^4–10^5	$>10^5$
ABO blood groups (F × M)		A × O O × A O × unknown	B × A (or O) AB × A (or O)	
Number of metastases	Nil	1–4	4–8	>8
Sites of metastases	Nil	Spleen Lung Vagina	GI tract Kidney	Brain Liver
Largest tumour mass	<3 cm	3–5 cm	>5 cm	
Previous chemotherapy	Nil		Single agent	Two or more drugs

(Low risk = 0–5; medium risk = 5–9; high risk = >9)

Modified from Bagshawe and Begent [7].

side is documented inadequately. We analysed our results with single agent etoposide in GTT to define its activity and update previously published data [4, 11].

PATIENTS AND METHODS

The records of 202 patients with GTT treated using single agent etoposide at Charing Cross Hospital were examined. Therapy for medium risk disease at our institution has commenced with single agent etoposide since 1978. A few patients with low and high risk disease also began their treatment with single agent etoposide due to incorrect initial prognostic scoring. In addition, other patients received etoposide after a variety of previous therapies.

(a) *Treatment protocol*

Etoposide was administered intravenously diluted in 250 ml of 0.9% saline over 30 min. From 1978 to 1983, 100 mg/m^2 was given daily for 5 consecutive days. Subsequently, 250 mg/m^2 was given on days 1 and 3 after equivalent pharmacokinetics had been demonstrated [12]. Other drugs (e.g. ACT-D, VCR, CTX) were administered sequentially after etoposide. A drug free interval of 6 days was allowed prior to the next course of treatment and this was extended if significant myelosuppression occurred.

(b) *Patient monitoring*

Serum human chorionic gonadotrophin (hCG) was measured at least twice weekly by automated radioimmunoassay using antiserum specific for the beta subunit of hCG capable of measuring 2 IU/l (0.5 ng/ml) [13]. All patients underwent regular clinical and radiologic assessment.

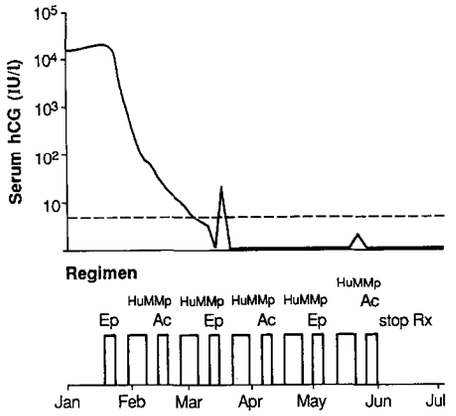

Fig. 1. Graphical illustration of typical hCG response after etoposide. EP = etoposide; HuMMp = hydroxyurea + methotrexate + 6-mercaptopurine; Ac = actinomycin D; hCG prior to day 1 etoposide (Ep) 20,490 IU/l, *hCG prior to day 1 next treatment (HuMMp)* 729 IU/l.

(c) *Response definition*

Response in GTT is measured by serum hCG concentration because this correlates so accurately with tumour behaviour [14]. Responses were defined by a fall in hCG concentration following etoposide. Partial response (PR) was recorded if hCG had fallen more than one log (i.e. >90%) from pretreatment level when measured immediately prior to the next course of chemotherapy (Fig. 1). Improvement (IMP) was recorded if hCG fell more than 50% but less than 90%. Stable disease (SD) implied no significant change in hCG (i.e. fall <50% or rise <10%). Progressive disease (PD) was defined by an increase greater than 10% in hCG level.

(d) *Definition of drug resistance*

The tumour was regarded as resistant to chemotherapy if hCG continued to rise on treatment or if levels plateaued and ceased to fall after initial

Table 2. Patients receiving single agent etoposide as initial chemotherapy for GTT

	Total	Low risk	Medium risk	High risk
Whole group	94	8	64	22
hCG response:				
PR	63 (67%)	5 (63%)	47 (73%)	11 (50%)
IMP	17 (18%)	0	11 (17%)	6 (27%)
SD	14 (15%)	3 (38%)	6 (9%)	5 (23%)
PD	0	0	0	0
Subsequent escalation to combination chemotherapy:	29 (31%)	1 (13%)	16 (25%)	12 (55%)
Completed chemotherapy, now alive and disease-free:	89	7	64	18
Still receiving chemotherapy <3 months from commencement:	2	1	0	1
Overall survival:	91 (97%)	8 (100%)	64 (100%)	19 (86%)

Median follow-up 63 months; range 2–106 months

response. Primary resistance is drug resistance at first exposure to an agent or combination while acquired resistance develops upon repeated exposure.

(e) *Statistical analysis*

Proportions were compared using chi square tests with Yates correction.

RESULTS

(a) *Patients treated first line with etoposide*

Of 101 patients treated first line with single agent etoposide, seven were excluded from further analysis because their hCG levels were falling after recent surgery (usually curettage) when etoposide was administered. All these patients showed continued decline in hCG after etoposide but it was not possible to ascribe this response solely to the drug. The remaining 94 patients were assessable. All had clearly progressive disease, 92 (98%) had received no prior chemotherapy and two (2%) sustained relapse after previous complete response to MTX but had received no antineoplastic treatment for at least 3 months when etoposide was administered. Twenty-two (23%) were high risk, 64 (68%) were medium risk and 8 (9%) were low risk (Table 2).

Sixty-three of these 94 patients (67%) fulfilled the criteria for PR and 17 (18%) for IMP. PR occurred more frequently in low risk (5/8, 63%) and medium risk patients (47/64, 73%) than in the high risk group (11/22, 50%; $P > 0.05$). Fourteen patients (15%) had SD after etoposide but 11 of these showed some fall in hCG level while marginally increased hCG (less than 7.5% above the pretreatment value) was noted in only three cases (two high risk, one medium risk). Hence, hCG levels actually fell after etoposide in 91 of 94 patients (97%). No PD was seen after etoposide. A transient rise in hCG several days after etoposide occurred frequently [69 of 87 patients (79%) where this information was available] but a net fall prior to the next chemotherapy course occurred subsequently in every case. This well recognised phenomenon may reflect rapid tumour lysis or differentiation of cytotrophoblast to syncytium [15].

Ninety (98%) of 92 assessable patients eventually achieved complete resolution of all disease, 88 with chemotherapy alone and another two with chemotherapy plus hysterectomy. Two patients (one high risk, one low risk) are still receiving chemotherapy but both are responding. Complete response was seen in 19 (90%) of 21 assessable high risk patients, all 64 medium risk patients and all seven assessable low risk patients. Ten patients (11%) relapsed subsequently; five of 19 (26%) high risk and five of 64 (8%) medium risk patients ($P > 0.05$). All responded completely to further chemotherapy and nine of these responses to re-treatment are sustained.

Twenty-nine (31%) of 94 patients commencing sequential treatment with single agent etoposide subsequently required intensive combination chemotherapy (EMA/CO [4]) because of drug resistance. They included 12 (55%) of 22 high risk patients and 16 (25%) of 64 medium risk patients ($P < 0.05$) and one of seven assessable low risk patients.

Eighty-nine (97%) of 92 patients who completed chemotherapy which commenced with single agent etoposide are alive, well and disease free at a median 63 months (range 2–106 months) from initiation of therapy. The other two patients remain on treatment less than two months since its commencement, but both are well and responding.

(b) *Patients treated with etoposide after resistance to prior chemotherapy*

Of 101 patients who had received prior chemotherapy when first treated with single agent etoposide, 62 were excluded from further analysis because hCG levels were falling already (46 cases) or because of previous etoposide-containing combination chemotherapy (16 cases). However, 39 had exhibited evidence of drug resistance and were analysed for etoposide activity in this setting. Twenty-three (59%) had received single agent MTX, one (3%) single agent ACT-D, 12 (31%) sequential MTX, ACT-D, VCR and CTX while three (8%) showed resistance to prior combination chemotherapy (CHAMOCA [7]). PR occurred in 18 (46%), IMP in 13 (33%) and SD in seven (18%) while only one progressed. In the group resistant to MTX, 18 (78%) of 23 sustained a fall in hCG after etoposide but none progressed. Since patients received different drugs at the next treatment, it is not possible to assume etoposide resistance with certainty in the SD group. One patient resistant to sequential therapy continued to progress after etoposide and died within 3 days of receiving the drug.

Of 37 previously drug resistant patients who have now completed chemotherapy, 34 (92%) remain alive and disease-free with median follow-up of 35 months (range 1–106 months). Another two are still receiving treatment within 2 months of first receiving etoposide but improvement is evident already.

(c) *Toxicity and deaths*

Because etoposide was administered in sequence with other agents of overlapping toxicity spectra, side-effects of etoposide in our patients cannot be defined precisely. The common problems of reversible alopecia and myelosuppression are well documented [11, 16]. In this group of patients using the etoposide doses prescribed, all patients were able to receive subsequent chemotherapy after a 6 day drug free interval so no delays for myelosuppression were necessary. Two cases of severe hypersensitivity to etoposide were observed with chest pain, fever, bronchospasm, urticaria and hypotension requiring intravenous fluids and corticosteroids. The drug was withdrawn from subsequent treatment in both patients.

Deaths are shown in Table 4. One patient died from neutropenic sepsis while receiving sequential chemotherapy for medium risk disease. She had responded to etoposide and the neutropenic episode leading to death did not occur after a course of etoposide. All the remaining deaths were due to progressive disease and multiple drug resistance. Of the two other deaths in the group whose chemotherapy commenced with etoposide, both occurred in patients with high risk disease. Both had progressed to receive combination chemotherapy but one never obtained a complete remission despite multiple different drug combinations. The second achieved complete remission but relapsed 4 months after finishing chemotherapy and eventually succumbed 21 months later without further complete remission despite extensive chemotherapy.

Table 3. Patients with established drug resistance treated with single agent etoposide (n = 39)

Previous chemotherapy:	
MTX	3 (59%)
ACT-D	1 (3%)
Sequential	12 (31%)
Combination	3 (8%)
hCG response to etoposide:	
PR	18 (46%)
IMP	13 (33%)
SD	7 (18%)
PD	1 (3%)
Overall survival	36 (92%)
Median follow-up 35 months; range 1–106 months	

Among previously treated patients, one death from progressive disease occurred 3 days after etoposide commenced and the two others at 3 and 12 months after improvement in hCG with single agent etoposide. Two of these deaths occurred in high risk patients and one in a medium risk patient; two patients were resistant to sequential chemotherapy and one to combination chemotherapy when etoposide was administered.

DISCUSSION

This study confirms the high activity of etoposide in GTT. HCG fell in 97% of patients who had not received prior chemotherapy and none progressed. Ninety-seven per cent survival in a group containing very few low risk patients (9%) attests to the value of etoposide containing regimens. Wong *et al.* reported similar results with single agent etoposide, given orally, in GTT [11] although their series contained fewer poor risk patients. HCG also fell significantly in 78% of patients with established resistance to previous therapy (which usually included MTX) and only one drug resistant patient progressed on etoposide. Overall survival of 92% in patients with documented drug resistance confirms the effectiveness of etoposide containing chemotherapy in GTT.

Because repeated cycles of single agent etoposide were not administered, it is impossible to speculate on the incidence of acquired etoposide resistance in GTT. Wong *et al.* reported low relapse rates after repeated cycles of single agent oral etoposide comparable with their experience after MTX alone [11]. None of our patients commencing chemotherapy with etoposide showed a sustained rise in hCG so

Table 4. Causes of death

	First line treatment group (n = 94)	Drug resistant group (n = 39)
Progressive disease	2 (both high risk)	3 (2 high, 1 medium risk)
Neutropenic sepsis	1 (high risk)	0
Total deaths	3 (3%)	3 (8%)

primary resistance does not appear a problem. Primary resistance to MTX is documented in a small number of cases [7] but overall experience with MTX is also much greater.

Toxicity specifically related to etoposide was difficult to assess in our series. Gonadal toxicity is a major consideration in management of females of reproductive age and Choo *et al.* reported significant temporary ovarian dysfunction among patients receiving intensive single agent etoposide [17]. However, we have observed successful conception in over 80% of patients treated with etoposide-containing combination chemotherapy and who wished to conceive subsequently [18]. Long term follow-up in patients treated with MTX suggests no gonadal toxicity is apparent with that drug [19].

Almost one-third of patients treated with sequential chemotherapy and over half the high risk patients receiving such treatment required subsequent more intensive combination chemotherapy because of drug resistance. Other data from this institution shows significant MTX resistance does occur in GTT, even in the low risk group [5]. Clearly, single agent MTX, or different single agents used sequentially, is not appropriate treatment for all patients with GTT. After careful prognostic scoring using established indices, we advocate initial sequential chemotherapy for patients in the medium risk group as this is less toxic than combination chemotherapy. We recognise that approximately 25% will require more intensive therapy subsequently. Excellent results have been obtained with EMA/CO [4] for patients in the high risk group using an intensive weekly schedule combined with prophylaxis against central nervous system involvement and the regimen is reasonably well tolerated [4, 5, 10].

Substitution of other active single agents, such as etopoide or ACT-D, is appropriate for low risk patient whose hCG has plateaued near normal (<50 IU/l) on MTX. Therapy for the small number of patients presenting with extremely advanced pulmonary, hepatic and central nervous system disease, in whom early death occurs due to tumour extent, remains a problem. The optimal intensity of initial chemotherapy in this group is unresolved. Cisplatin, the principal active agent not included in EMA/CO, may have a role in this context.

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