Protracted oral etoposide in epithelial ovarian cancer: a phase II study in patients with relapsed or platinum-resistant disease

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Summary This phase II study evaluates the efficacy and toxicity of a prolonged schedule of oral etoposide in patients with measurable advanced ovarian cancer resistant to, or relapsed following, platinum-based chemotherapy. Forty-seven patients participated, 20 of whom had received more than one prior treatment. Seventy-seven per cent had evidence of disease progression during or within 6 months of the previous chemotherapy. Initially, oral etoposide, 50 mg b.d. (regardless of patient size), was given for 14 days on a 21-day cycle. However, after encountering toxicity, the schedule was modified to 7 days’ treatment escalating to 10 then 14 days if well tolerated. Among 41 assessable patients there were two complete and eight partial objective responses (24% response rate; 95% confidence interval 12–41%). Nine further patients (22%) had stable disease, four with a sustained fall of >50% in CA-125. Median duration of response or stable disease was 3 months (range 1–49). Overall median survival was 41 months from study entry (range 2 to 96+ weeks).

Toxicity for most patients was mild, but sporadic severe myelotoxicity occurred, with two treatment-related deaths. Risk factors for severe toxicity were: performance status 3; hepatic impairment; renal impairment. We conclude that oral etoposide has activity in platinum-resistant ovarian cancer and that it is a useful palliative therapy. It has significant toxicity which may be avoided by appropriate patient selection and an escalating-duraton schedule.

Platinum-based chemotherapy protocols have high initial response rates in patients with epithelial ovarian cancer. However, when the disease is primarily resistant, or when relapse occurs within a year, the prospects for second-line treatment are bleak. Phase II studies in this situation, either with single agents (Sutton et al., 1989; Coleman et al., 1989; 1990; Manetta et al., 1990) or with combination chemotherapy (Belinson et al., 1986; Benedetti-Panici et al., 1990; Pater et al., 1987), have generally yielded few responses, of short duration. Even the promising new agent, taxol, gives responses in only 20–30% of this group of patients (Einzig et al., 1992; McGuire et al., 1989; Trimble et al., 1993).

Platinum-resistant cell lines show little or no cross-resistance to etoposide in vitro, making it a potential candidate for use either in combination with platinum as primary treatment or, later, as second-line treatment for this disease. In the five previously reported studies using single-agent etoposide as second-line treatment, a total of 247 patients were treated, with 51 responses (complete and partial responses; 21%). These studies all employed 3 or 4 day intravenous or oral schedules (Kuhne et al., 1988; Kavanagh et al., 1989; Eckhardt et al., 1990; Hillecoat et al., 1985; Hansen et al., 1990).

Etoposide interacts with topoisomerase II, which is active during the late S and early G2 phases of the cell cycle. It is consequently schedule dependent in vitro (Hill et al., 1981), and studies in small cell lung cancer (SCLC) have also demonstrated marked clinical schedule dependency: when a total dose of 500 mg m⁻² was given either as a single 24 h i.v. infusion or divided into five daily fractions, the response rates to single day and 5 day treatments were 10% and 90% respectively (Slevin et al., 1989a). A subsequent study comparing the same total dose given intravenously over either 5 days or 8 days suggested some further benefit in terms of reduced myelotoxicity with the longer schedule (Slevin et al., 1989b). Protracted oral schedules have subsequently given good response rates in SCLC and are generally well tolerated (Clark et al., 1990). Furthermore, responses to protracted oral etoposide have been seen in patients with SCLC and germ cell tumours which had previously progressed through combination chemotherapy including etoposide (Greco et al., 1990; Miller & Einhorn, 1990).

For these reasons we elected to re-evaluate etoposide in the treatment of epithelial ovarian cancer using a prolonged oral administration schedule. The setting chosen was a multi-institutional phase II study for patients with relapsed disease, previously treated with at least one platinum-based regimen. The schedule chosen was one of those previously used in non-pretreated small cell lung cancer patients: 50 mg b.d. for 14 days on a 3 week cycle (Clark et al., 1990). This protocol subsequently had to be modified because of toxicity.

Patients and methods

This prospective study was initiated in November 1990 by the London Gynaecological Oncology Group (LGOG). Patients were treated by medical oncologists at St. George’s Hospital, London; The Royal London Hospital, London; St. Bartholomew’s Hospital, London; The Royal Marsden Hospital, London; Guy’s Hospital, London; and Queen Mary’s Hospital, Sidcup, Kent, UK. The study was approved by the Clinical Research Ethics Committees of these institutions. Patients were informed of the investigational nature of the treatment and of its expected toxicities before giving written consent.

Eligibility criteria

To be eligible, patients were required to have assessable, histologically confirmed epithelial ovarian cancer with radiological and/or clinical evidence of disease progression during the preceding 2 months. Previous treatment with at least one platinum-containing regimen was mandatory and the treating physician had to be satisfied that further platinum-based treatment was inappropriate. The protocol required an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 at study entry, however five patients with ECOG status 3 were entered (all of whom fared badly) and have been included in the analysis. A granulocyte

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count of \(1.5 \times 10^9\) l\(^{-1}\) and platelet count of \(100 \times 10^9\) l\(^{-1}\) were required. Patients with serum bilirubin > 30 \(\mu\)mol l\(^{-1}\) were ineligible, as were those with unresolved bowel obstruction or other impediment to oral therapy. Age and renal function were not limited but, in accordance with previous data on the effect of renal function on etoposide pharmacokinetics and toxicity, a dose reduction was made if serum creatinine exceeded 130 \(\mu\)mol l\(^{-1}\) (Joel et al., 1991a). One patient with renal impairment had a pharmacokinetics-guided dose reduction and received 50 mg o.d. alternating with b.d. (see below).

**Treatment and monitoring**

Soft gelatin etoposide 50 mg capsules were used, which also contain glycerol and polyethylene glycol (Bristol Myers Pharmaceuticals, UK). Initially, the starting dose was 50 mg b.d. for 14 days but, following four occurrences of WHO grade 4 myelotoxicity with one treatment-related death among the first 13 patients, the protocol was modified. Subsequent patients received 50 mg b.d. for 7 days in cycle 1, 10 days in cycle 2 and 14 days in cycles 3–6, each escalation being made only if no toxicity of grade 3–4 had occurred.

Treatment was given on a 21 day cycle, to a maximum of six cycles. The cycle was delayed 1 week if the granulocyte count was <1.5 \(\times 10^9\) l\(^{-1}\) or the platelet count was <100 \(\times 10^9\) l\(^{-1}\) on day 1. The full blood count was repeated on day 8 and day 15 of each cycle. Patients were interviewed and examined on day 1 of each treatment cycle and non-haematological toxicity was recorded using World Health Organization (WHO) criteria (WHO, 1979).

Patient compliance was not formally assessed, but alopecia was observed in all patients who completed two or more treatment cycles. A previous study of compliance with the same schedule of oral etoposide in small cell lung cancer patients demonstrated overall compliance of >90% (Lee et al., 1993).

The response to etoposide treatment was assessed radiologically (using CT scan) after the third and sixth cycles, or sooner in the event of clinical deterioration. Patients with a response or stable disease were reassessed at intervals not exceeding 3 monthly during follow-up. Tumour responses were classified in accordance with WHO criteria (WHO, 1979). The time to treatment failure was defined, in line with these criteria, as the duration from the start of etoposide treatment to the detection of disease progression. CA-125 measurements were made in all patients before and during treatment and were used to guide clinical investigation but not, in isolation, to determine response status. Patients were deemed unassessable for response if, in the absence of any indication of disease progression, treatment had to be stopped after the first course.

**Statistical design**

Standard phase II stopping rules were in force, using Gehan’s plan to stop accrual if the probability of the response rate being over 20% fell below 5% (Simon, 1989). These stopping rules did not need to be applied.

**Results**

Between November 1990 and January 1993, 47 patients were entered onto this study (see Table I). All are evaluated for toxicity but six are not evaluable for response, one because the marker lesion on CT scan later turned out to be a bladder diverticulum, the others because of withdrawal after the first cycle, without evidence of disease progression, because of toxicity (three patients) or for personal reasons (two patients). Sixty per cent of patients had involvement of the liver parenchyma or distant sites. For the purposes of comparison with other phase II studies, data are presented both for the interval to disease progression following the most recent chemotherapy and for the treatment-free interval before starting oral etoposide. The study is now mature, with only 14 patients remaining alive, three without disease progression.

### Table I  Patient characteristics

| Total entered | 47 |
|---|---|
| Assessable for response | 41 |
| Age: median (range) | 60 (41–76) |
| Sites of disease at study entry | |
| Pelvis/peritoneal cavity | 43 (91%) |
| Retroperitoneal | 22 (47%) |
| Liver parenchyma/distant | 28 (60%) |
| Performance status (ECOG) | |
| 0 | 10 (21%) |
| 1 | 26 (55%) |
| 2 | 6 (13%) |
| 3 | 5 (11%) |
| Prior therapy | |
| Cis- and/or carboplatin | 47 (100%) |
| Other cytotoxics | 9 (19%) |
| Radiotherapy | 8 (17%) |
| No. of previous chemotherapy protocols | |
| 1 | 27 (57%) |
| 2 or 3 | 20 (43%) |
| Time to PD after last chemotherapy | |
| 0 (PD on treatment) | 16 (34%) |
| 1–6 months | 20 (43%) |
| >6 months | 11 (23%) |
| Treatment-free interval | |
| <6 months | 28 (60%) |
| >6 months | 19 (40%) |

| Table II  Characteristics of patients with CR, PR or SD (n = 19) |
|---|---|
| Age: median (range) | 60 (41–67) |
| Sites of disease | |
| Pelvis/peritoneal cavity | 17 (89%) |
| Retroperitoneal | 3 (16%) |
| Liver parenchyma/distant sites | 7 (37%) |
| Performance status at entry | |
| 0 | 7 (37%) |
| 1 | 12 (63%) |
| 2 or more | 0 |
| No. of previous chemotherapy protocols | |
| 1 | 9 (47%) |
| 2 or 3 | 10 (53%) |
| Time to PD after last chemotherapy | |
| 0 (PD on treatment) | 5 (26%) |
| 1–6 months | 10 (53%) |
| >6 months | 4 (21%) |
| Treatment-free interval | |
| <6 months | 9 (47%) |
| >6 months | 10 (53%) |
by $>50\%$ fall or complete normalisation of serum CA-125.
PR durations were 49, 39, 35, 32, 28, 27 24+ and 21 weeks.
In addition, stable disease or lesser response (SD) lasting
16–45 weeks was seen in a further nine patients, four of
whom had a sustained fall of $>50\%$ in serum CA-125.

The median time to treatment failure for patients with CR,
PR or SD is 35 weeks. The characteristics of these 19
patients are summarised in Table II. It is of note that re-
sponses and SD were only seen in patients with performance
status 0 or 1.

Survival
Median survival for all 47 patients was 41 weeks (range
2–96+ weeks). As expected, among the assessable patients,
disease response or SD was associated with increased sur-
ival, with median survival projected at 81 weeks compared
with 24 weeks for those with progressive disease (PD) (Figure
1), although of course this is not proof of a causal relation-
ship. Patients with an objective response did not fare
significantly better than those with stable disease.

Toxicity and protocol modification
The toxicities recorded in all 47 patients are shown in Table
III. Variable and excessive toxicity was encountered during
treatment of the first 13 patients at a starting dose of
50 mg b.d. for 14 days: four patients developed grade 4
myelotoxicity, one of whom died. These patients all carried
risk factors of age, poor performance status or hepatic
impairment (Table IV). Thereafter the protocol was modified
and subsequent patients received only 7 days’ treatment for
the first cycle, escalating to 10 then 14 days only if no grade
3 or 4 toxicity was encountered. Of 34 patients treated on
this escalating schedule, 17 (50\%) reached the full 14 day
regimen. The others continued on a 7 day (six patients) or 10
day (five patients) schedule, or had been withdrawn before
full escalation could occur. Inability to tolerate the full 14
day schedule correlated with age, performance status and
number of previous treatments, but not with mild renal or
hepatic dysfunction.

After this protocol modification, only two of 34 patients,
one with severe renal impairment, developed grade 4
myelotoxicity, and treatment was generally well tolerated.
The patient with renal impairment (glomerular filtration rate
14 ml min$^{-1}$) was also hypobulminenaemic (29 g l$^{-1}$). She
was given a test dose on day 1, following which total plasma
etoposide pharmacokinetics was measured using a limited
sampling strategy described elsewhere (Joel et al., 1991b). A
dose reduction was calculated and a further 6 days’ treatment
was given at 50 mg o.d./b.d. on alternate days. Further sam-
pling on day 7 confirmed that drug accumulation had not
occurred. However, despite this, grade 4 myelotoxicity
developed from day 11, complicated by Staphylococcus
aureus sepsicaemia, and the patient subsequently died.

Response in relation to toxicity and dose intensity
Taking all 41 assessable patients (original + modified pro-
tocols), there is no correlation between the highest grade of
myelotoxicity and the response to treatment (overall $\chi^2$
$P = 0.9$). Thus, responses and disease stabilisation were seen
as commonly in patients who had only grade 0–1 myeloto-
xicity as in those showing significant myelotoxicity during
treatment.

For patients on the modified protocol, there was a rela-
tionship between the ability to escalate to the full 14 day
schedule and the subsequent response. One CR and two SD
were seen among the 11 patients who could not tolerate the
full 14 day regimen (response + SD = 21\%), compared with
one CR, seven PR and four SD among the 17 who could
(response + SD = 70\%). However, this difference might
relate to the poorer performance status of the former group
rather than to the lower dose intensity received.

Discussion
This study demonstrates that oral etoposide has activity in
relapsed ovarian cancer. In this population of patients with
bulky and multiple sites of disease the objective response rate
of 24\% (95\% confidence interval 12–41\%) is encouraging.
This experience is superior to that of Marzola et al. (1993),
who recently reported only one PR among 17 patients using
oral etoposide 50 mg o.d. for 21 days every 4 weeks. Their
patients were more heavily pretreated (all $\geq 2$ previous
treatments), but of better performance status (all 0–1) and
with a longer treatment-free interval (>6 months in 55\%). It
is possible that the lower dose intensity of the 50 mg o.d.
schedule was a factor.

| Table III | Worst toxicity |
|---|---|
| Toxicity (n = 47 patients) | WHO grade |
| | 0 | 1 | 2 | 3 | 4 |
| Haematological | 12 | 11 | 9 | 9 | 6 |
| Infection | 43 | 0 | 0 | 2 | 2$^a$ |
| Nausea/vomiting | 15 | 18 | 8 | 4 | 2$^a$ |
| Stomatitis | 29 | 5 | 9 | 2$^a$ | 2$^a$ |
| Alopecia in all patients – not graded | | | | |
| No other toxicities $>\text{grade 2}$ | | | |

Total 194 treatment cycles administered. $^a$ Died from sepsis during
nadir. $^a$ Patients with PD and bowel obstruction. $^a$ In association with
neutropenia.

| Table IV | Characteristics of patients with severe first-cycle toxicity |
|---|---|
| Age | Performance status | Renal impairment | Hepatic impairment | Cycle I duration | Haematological toxicity | Mucosal toxicity | Outcome |
|---|---|---|---|---|---|---|---|
| 56 | 3 | -- | + | 14 days | 4 | 4 | Toxic death |
| 67 | 3 | + | + | 7 days | 4 | 0 | Toxic death |
| 47 | 3 | -- | -- | 14 days | 4 | 0 | Withdrawn (PD) |
| 56 | 2 | -- | + | 14 days | 4 | 3 | Withdrawn (toxicity) |
| 76 | 1 | -- | -- | 14 days | 4 | 3 | Withdrawn (toxicity) |
The result of this study should be interpreted in the light of the published phase II studies of taxol in relapsed ovarian cancer (Einzig et al., 1992; McGuire et al., 1989), in which a total of 70 patients have been treated with two complete and 16 partial responses (CR + PR 26%); 95% confidence intervals 16–38%). One of these studies excluded patients with more than one previous chemotherapy treatment. Data recently reported from the use of taxol in very heavily pretreated patients (≥3 prior regimens) throughout the USA suggested a response rate of 21%, with 19% SD (Trimble et al., 1993).

Whether etoposide’s activity is clinically useful depends on the balance of treatment-induced toxicity against antitumour activity; a judgement that must be made for individual patients. The consistent side effect of etoposide is alopecia which, for some but not all patients, is an important price to pay for a modest chance of benefit. For many patients this was the only significant side effect, but more worrying were the episodes of severe myelotoxicity, with two treatment-related deaths. All the affected patients had one or more risk factors: performance status ≥3; moderate/severe hepatic or renal impairment, age over 75. The incidence of severe toxicity is minimised by avoiding patients with these risk factors and using the escalating schedule.

Haematopoietic growth factors were not used during this study, and three observations suggest that the routine use of granulocyte or granulocyte–macrophage colony-stimulating factor for ‘poor-risk’ patients would not have been helpful:

1. The risk factors for toxicity appeared also to predict for failure to respond.
2. Severe neutropenia, when it occurred, was accompanied by thrombocytopenia.
3. Response did not correlate positively with myelotoxicity overall.

A policy of patient selection to avoid severe toxicity would therefore seem more appropriate than one of ‘treat and rescue’. However, growth factors may, of course, be appropriate in cases of unexpected severe neutropenia.

Etoposide’s oral bioavailability shows marked inter- and intra-patient variability (Harvey et al., 1985). Once absorbed, it is largely bound to plasma proteins, with free drug being cleared by both renal and hepatic routes. There is therefore much potential net variability in the pharmacokinetics of the drug in cancer patients, who may have altered gastrointestinal function, hypoproteinaemia and hepatic or renal dysfunction. Pharmacokinetic monitoring and dose adjustment in our patient with renal impairment failed to prevent excessive toxicity, however hypoalbuminaemia with consequently reduced protein binding may have confounded the pharmacokinetic monitoring in this case.

The stimulus to the development of protracted oral etoposide schedules is the hypothesis that, in small cell lung cancer, a pharmacodynamic relationship exists between etoposide’s anti-tumour activity and the duration for which plasma levels are maintained above a low threshold value in the region of 1 µg ml⁻¹ (Slevin, 1990). The schedule of 50 mg b.d. used in this study produces plasma etoposide > 1 µg ml⁻¹ for a median of 14 h out of every 24 (Joel et al., 1991b). However, the prolonged drug exposure provided in this study has not resulted in improved activity compared with previous reports of 3 or 4 day intravenous or oral schedules (Kuhnle et al., 1988; Kavanagh et al., 1989; Eckhardt et al., 1990; Hillcoat et al., 1985; Hansen et al., 1990). There are several possible explanations for this:

1. A 4 day schedule may be long enough to exploit fully any schedule dependency of etoposide in ovarian cancer, with no additional benefit from more prolonged scheduling.
2. The patient population may be different: the largest and most optimistic study of intravenous etoposide was in patients with only one previous chemotherapy exposure (Kuhnle et al., 1989).
3. The variable oral bioavailability of etoposide may result in failure to reach the threshold concentration for activity in a proportion of the patients. Continuous ambulatory intravenous infusion would provide a superior, if less convenient, means of maintaining consistent prolonged low plasma levels (Greco et al., 1992).

In conclusion, oral etoposide has significant activity against relapsed and platinum-resistant ovarian cancer and bears comparison with the best alternative intravenous therapies. It should be employed with caution: patients who are elderly, of poor performance status or with moderate to severe hepatic or renal impairment may suffer severe myelotoxicity, not necessarily preventable by pharmacokinetic-guided dose adjustment, and are in any case unlikely to benefit from treatment. Conversely, relatively fit patients may benefit from this outpatient treatment, whose main toxicity when properly monitored is reversible alopecia. Continuous ambulatory intravenous infusion of etoposide is an alternative means of providing optimal prolonged-schedule therapy and is currently under investigation.

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PROTRACED ORAL ETOPOSIDE FOR OVARIAN CANCER

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