Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma

W. ten Bokkel Huinink1*, S. R. Lane2 & G. A. Ross2
On behalf of the International Topotecan Study Group

1The Netherlands Cancer Institute, Amsterdam, The Netherlands; 2GlaxoSmithKline, Collegeville, PA, USA and Harlow, UK

Received 22 May 2003; revised 22 August 2003; accepted 17 September 2003

Background: We have continued to monitor the survival of patients randomised in a previously reported multicentre phase III study of topotecan versus paclitaxel in patients with advanced epithelial ovarian cancer who had failed one prior platinum-based regimen.

Patients and methods: Patients with bidimensionally measurable disease were randomised to topotecan (1.5 mg/m2/day for 5 days) or paclitaxel (175 mg/m2/day as a 3-h infusion) every 21 days. Patients were eligible for treatment with the alternate therapy at third line. The European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QOL)-C30 questionnaire was also used to measure eight symptoms at baseline and during each course (pain, anorexia, diarrhoea, fatigue, nausea and vomiting, dyspnea, constipation and insomnia).

Results: A total of 226 patients were evaluable for response. Demographic characteristics were similar in both treatment groups, as were results of the EORTC QOL-30 questionnaire. For the topotecan group, median time to progression was 18.9 weeks (range <1 to 92.6+ weeks; 25% censored), and, for paclitaxel, 14.7 weeks (range <1 to 137.3+ weeks; 12.3% censored); P = 0.076. At 4 years post-randomisation, median survival in the topotecan group was 63.0 weeks (range <1 to 238.4+ weeks; 20.5% censored) and, for paclitaxel, 53.0 weeks (range <1 to 226.3+ weeks; 12.3% censored); P = 0.44.

Conclusion: Topotecan continues to demonstrate comparable efficacy and survival to paclitaxel with manageable and non-cumulative haematological toxicity. Non-haematological toxicity was generally mild for both groups. The long-term survival rate indicates substantial therapeutic benefit for this group of patients receiving topotecan at relapse of ovarian cancer.

Key words: ovarian carcinoma, paclitaxel, platinum, topotecan

Introduction

Over the past decade, the two drugs most extensively studied in relapsed ovarian cancer have been paclitaxel and topotecan [1–4]. When given as second-line therapy, these two agents have similar activity, as evidenced by a 20% response rate for topotecan and 13% for paclitaxel [1]; a recent clinical trial has also reported similar rates for topotecan when compared with pegylated liposomal doxorubicin [3].

Data from multicentre randomised phase III studies of topotecan and paclitaxel provide an opportunity to demonstrate long-term survival benefit, including in patients who have crossed-over to receive the alternate agent as third-line treatment [1, 4].

We have continued to monitor progression-free survival and overall survival of patients in a previously reported multicentre, randomised phase III study of topotecan versus paclitaxel in patients with advanced epithelial ovarian cancer who had failed one prior platinum-based regimen [1].

Patients and methods

Randomisation, treatment and events measured

Patients with bidimensionally measurable disease (≥2 cm) who had progressed during or after treatment with one platinum-based chemotherapy regimen were randomised to topotecan 1.5 mg/m2/day as a 30-min infusion or paclitaxel 175 mg/m2/day as a 3-h infusion every 21 days. At the discretion of the investigator, patients could be crossed-over to receive the alternate drug as third-line therapy. Demographic details of the patient population for both the randomised and cross-over studies have been reported [1, 4]. The majority of patients in each group had a performance status of 0–1.

After the end of first-line platinum therapy, patient sensitivity to platinum was reported as refractory (progression during chemotherapy) or disease relapse, with relapse further categorised as early (within 3 months), interim (between 3 and 6 months), or late (≥6 months).

In both the second-line and third-line treatment studies, primary efficacy measures were response rate, duration of response, and time to progression.
according to World Health Organisation (WHO) criteria [5]. Responses were independently reviewed and confirmed by a radiologist blinded to the treatment received. Time to response and overall survival, the secondary efficacy measures, were assessed from time of initial second-line or third-line drug administration to progressive disease or death, respectively. Haematological and non-haematological toxicities were assessed utilising the National Cancer Institute common toxicity criteria.

Qualitative assessments
Patients were administered the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QOL)-C30 questionnaire to assess pain, anorexia, diarrhoea, fatigue, nausea and vomiting, dyspnea, constipation and insomnia.

Statistical analysis
For the purposes of this updated analysis, Kaplan–Meier estimates were obtained for each patient for time to progression and survival; the Cox regression model was used to compare these end points between treatment groups. For patients who received topotecan relative to paclitaxel, results were calculated as a hazards ratio with a 95% confidence interval.

Results
A total of 226 patients who were first-line platinum failures were evaluable for response; 112 were randomised to topotecan and 114 to paclitaxel. As has been reported previously, demographic characteristics were similar in both treatment groups [1].

Time to progression was 18.9 weeks (range <1 to 92.6+ weeks; 25% censored) for the topotecan group and 14.7 weeks (range <1 to 137.3+ weeks; 12.3% censored) for the paclitaxel group ($P = 0.08$).

Survival was 63.0 weeks (range <1 to 238.4+ weeks; 20.5% censored) for the topotecan group and 53.0 weeks (range <1 to 226.3+ weeks; 12.3% censored) for the paclitaxel group ($P = 0.44$). Quality of life was reported using individual factors, such as pain and fatigue, from the EORTC QOL-C30 questionnaire and measured changes from baseline to end of best response. Between 75% and 85% of patients who enrolled in the study had evaluable quality of life data. The EORTC QOL-C30 questionnaire results for pain, anorexia, diarrhoea, fatigue, nausea and vomiting, dyspnea, constipation and insomnia were similar for the two groups, and treatment with either topotecan or paclitaxel was not associated with any compromise of quality of life of the patients.

Long-term survival
Follow-up data from this trial have now been collected for more than 4 years. For the topotecan group, median follow-up is 20.8 (range 0–86) weeks; for the paclitaxel group, median follow-up is 23.6 (range 0–117) weeks. Both the topotecan and paclitaxel treatment arms continue to provide long-term survival benefit. The updated survival curves are shown in Figure 1.

Topotecan versus paclitaxel
Median survival for patients receiving topotecan remains constant at 63 weeks. The median survival for paclitaxel-treated patients is 53 weeks (log-rank $P = 0.44$).

When the topotecan arm was stratified by platinum sensitivity, the Kaplan–Meier plot revealed survival distributions of patients who were refractory (34 patients; number censored, 8), early/interim relapse (26 patients; number censored, 4) and late relapse (52 patients; number censored, 11) to be significantly different between each group ($P = 0.02$) (Figure 2A).

Similarly, when the paclitaxel arm was stratified by platinum sensitivity, the Kaplan–Meier plot found survival distributions of patients who were refractory (33 patients; number censored, 4), early/interim relapse (26 patients; number censored, 2) and late relapse (52 patients; number censored, 11) to be significantly different between each group ($P = 0.02$) (Figure 2B).
relapse (54 patients; number censored, 8) to be significantly different ($P = 0.0004$) (Figure 2B).

**Non-cross-resistance**

In this study, patients were eligible for treatment with the alternate therapy at third-line, usually for one of three reasons: failure to respond to second-line therapy, relapse after an initial response to second-line therapy, or toxicity.

Demographic characteristics were similar between the two groups who crossed-over to third-line therapy [4]. A total of 110 patients received the alternate drug (61 topotecan, 49 paclitaxel). Response rates of 13.1% for topotecan (eight of 61) and 10.2% for paclitaxel (five of 49) were demonstrated. Seven patients who failed to respond to second-line treatment with paclitaxel responded to topotecan third-line, as did four to paclitaxel third-line [3], demonstrating a degree of non-cross-resistance.

**Haematological and non-haematological toxicity**

The principal adverse effect seen in all patients was myelosuppression; specifically, grade 4 neutropenia, which was observed in 79% of topotecan and 23% of paclitaxel patients receiving second-line therapy, and 81% of topotecan and 23% of paclitaxel patients who received third-line therapy. In the topotecan group, the highest incidence of grade 4 neutropenia was observed during the first course (57% of all patients during second-line treatment and 59.3% during third-line treatment); this decreased in subsequent courses. Grade 4 thrombocytopenia was also higher in patients who received topotecan than paclitaxel in both second-line and third-line treatment regimens. In the topotecan-treated group, myelosuppression was non-cumulative, manageable and resolved quickly (nadir 5–7 days). Requirements for additional symptomatic treatment were limited, as were sequelae.

For the topotecan group, non-haematological toxicity consisting primarily of gastrointestinal disturbances (nausea, vomiting, diarrhoea, constipation) was generally mild or moderate (grade 1/2). No end organ toxicities, such as cardiac, neurological, skin or otorrheic, were observed and all non-haematological toxicities were non-cumulative.

**Discussion**

Topotecan was first approved in 1996 for the treatment of relapsed ovarian cancer and is now approved in more than 70 countries worldwide. This approval was based on three non-comparative phase II trials [6–8] and one phase III trial comparing topotecan with paclitaxel [1]. The efficacy of topotecan has been further demonstrated in two large, phase III randomised trials, one comparing intravenous with oral topotecan [2] and one comparing topotecan and pegylated liposomal doxorubicin [3]. Efficacy with regard to response rate, time to progression and survival has also been demonstrated in both platinum-sensitive [1] and paclitaxel-resistant [9] disease. Topotecan has demonstrated a high overall objective response and relatively low toxicity in patients treated at first relapse who were sensitive to first-line therapy.

Clinical trials of topotecan have been conducted using rigorous definitions of response rate and stable disease [10]. In a retrospective study that examined response in relation to survival in 506 patients with ovarian cancer who received topotecan or paclitaxel as second-line therapy, results of individual patient level data failed to show any meaningful difference between partial response (PR) and disease stabilisation (SD; i.e. lasting >8 weeks) by the stringent criteria used in the protocol. Lack of objective tumor regression alone, therefore, should not be cause for premature discontinuation of a treatment regimen [10]. The sum of PR and SD (40–50%) is a reflection of the proportion of patients deriving clinical benefit from therapy.

A large phase III comparative trial of topotecan versus pegylated liposomal doxorubicin demonstrated similar overall efficacy (response rate and survival), with differing toxicity profile [3]. Patients who received topotecan reported significantly less pain than those who received pegylated liposomal doxorubicin (81% versus 64%). This was believed to be associated with palmar–plantar erythrodysesthesia (PPE), which occurred in 40% of patients treated with pegylated liposomal doxorubicin and was severe (grade 3/4) in 23% of patients. Emotional functioning was also higher in the topotecan group (74% versus 67%) [11]. No late toxicities were observed.

Although a subgroup analysis of platinum-sensitive patients showed an increase in overall survival following therapy with pegylated liposomal doxorubicin, lack of follow-up of patients to determine what additional treatment they might have received after removal from the study may have confounded these results, and data on third-line therapies were not collected. In addition, those who received topotecan during the study would have been unlikely to have subsequently received pegylated liposomal doxorubicin, since it was not then approved for the treatment of ovarian cancer [3]. Long-term data for the pegylated liposomal doxorubicin group are not available.

As this updated time to progression and survival analysis of one of the longest trials to date for relapsed ovarian cancer has shown, topotecan continues to demonstrate comparable efficacy and survival when compared with paclitaxel. Haematological toxicity is non-cumulative and manageable; non-haematological toxicity is generally mild for both groups. The long-term survival rate of 20% at 4 years indicates substantial therapeutic benefit for this group of patients receiving therapy at relapse of ovarian cancer. The gain in survival was not achieved at the expense of quality of life, as measured by the EORTC QOL-C30 instrument, which showed quality of life to be consistent throughout therapy. This supports the rationale for incorporating topotecan and paclitaxel in combination or sequentially in future first-line regimens, especially given the degree of non-cross-resistance shown in this study.

**References**
