Topotecan as Second-Line Therapy for Ovarian Cancer: Dosage Versus Toxicity

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Abstract
In this issue of The Oncologist, Armstrong et al. present an analysis of the use of topotecan (Hycamtin®; GlaxoSmithKline, Philadelphia, http://www.gsk.com) in the second-line treatment of both ovarian cancer and small cell carcinoma of the lung. This cytotoxic agent has clearly been demonstrated to be a useful drug in a population of patients with both of these conditions. However, the description of the nature of the toxicity, as stated in the manuscript, must be questioned along with comments made regarding the relative toxicity of alternative cytotoxic agents frequently used in similar settings. The purpose of this discussion absolutely is not to negate the unquestioned, demonstrated usefulness of topotecan as second-line therapy in ovarian cancer but rather to point out that the U.S. Food and Drug Administration–approved dose level of 1.5 mg/m² per day × 5 days can cause substantial and highly clinically relevant bone marrow toxicity. Whether this toxicity, which can result in a level of fatigue that may cause responding patients to discontinue treatment, should simply be labeled “excessive” rather than “cumulative” appears to be a matter of semantics rather than an important distinction. Whether delivery of a lower dose of topotecan (1 mg/m²–1.25 mg/m² per day × 5 days) will essentially eliminate concern for the development of severe clinically relevant marrow toxicity is uncertain, but the risk will certainly be substantially reduced. The Oncologist 2005;10:695–697

In this issue of The Oncologist, Armstrong et al. [1] present an analysis of the use of topotecan (Hycamtin®; GlaxoSmithKline, Philadelphia, http://www.gsk.com) in the second-line treatment of both ovarian cancer and small cell carcinoma of the lung. This cytotoxic agent has clearly been demonstrated to be a useful drug in a population of patients with both of these conditions. As noted in this review, perhaps the most attractive feature associated with the administration of topotecan is the rather impressively limited nature of its toxicity profile, with depression of bone marrow elements being, in the large majority of treated patients, its only important side effect.

However, the description of the nature of the toxicity, as stated in the aforementioned manuscript, must be questioned along with comments made regarding the relative toxicity of alternative cytotoxic agents frequently used in similar settings.

In the discussion, Armstrong, et al. [1] state that “the generally manageable hematologic toxicity profile of topotecan suggests that topotecan may be safely administered for multiple courses or potentially until disease progression.” While this statement is accurate for many patients, it is certainly not the universal experience, as reported in the peer-reviewed literature.
The review itself notes that red cell transfusions were administered to 52% of patients receiving topotecan and that suspected or documented sepsis or infections and grade 4 thrombocytopenia were observed in 23% and 27% of patients, respectively. It is unclear if the well-documented side-effect profile, when topotecan is used as second-line therapy of ovarian cancer at the U.S. Food and Drug Administration (FDA)—approved dose level of 1.5 mg/m² per day (× 5 days), can justify the use of the description used by Armstrong et al. [1] that the hematologic toxicity is “generally manageable” and that the drug “may be safely administered for multiple courses.”

In fact, as reported by the Gynecologic Oncology Group in a paper quite relevant to the current discussion, five patients participating in a phase II trial of single-agent topotecan, administered as second-line therapy of ovarian cancer, discontinued therapy as a result of severe treatment-related fatigue despite being responders to the treatment program [2]. As will be noted later in this commentary, it is likely that it was the dose of topotecan used in that trial (1.5 mg/m² per day × 5 days), rather than the drug itself, that was principally responsible for the severity of this highly clinically relevant side effect of treatment.

Another less definitive but provocative experience also raises an important challenge to the Armstrong et al. [1] statement regarding the impact of topotecan-associated hematologic toxicity. In the previously reported randomized phase III trial (unfortunately not referenced in the Armstrong et al. [1] paper), which directly compared single-agent topotecan with liposomal doxorubicin (Doxil®; Alza Pharmaceuticals, Mountain View, CA, http://www.alza.com) as “second-line treatment” of ovarian cancer, while there was no difference in the objective response rate (28.4% versus 28.8%) and only a very small difference in progression-free survival (median, 28.9 weeks versus 23.3 weeks) in favor of the liposomal doxorubicin in the “platinum-sensitive” patient population, there was a far greater difference in overall survival in this study subset, in favor of liposomal doxorubicin (median, 108 weeks versus 71.1 weeks) [3].

In that trial, critically relevant data on third-line treatment (after discontinuation of study therapy) for the patient populations were apparently not collected. Therefore, it is not possible to draw any definitive conclusions regarding what happened after either the topotecan or liposomal doxorubicin was stopped.

However, one reasonable interpretation of the striking finding of this substantial variance between the impact of liposomal doxorubicin on progression-free (5.6 weeks) versus overall survival (36.9 weeks) is the potential difference between what happened to the patients after they finished treatment with either the topotecan or liposomal doxorubicin. Because these patients remained theoretically “sensitive to platinum” (as defined in the protocol, platinum-free interval of >6 months), it is logical that a patient’s oncologist would have attempted to re-treat with a platinum agent (most likely carboplatin [Paraplatin®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com]).

However, if patients previously treated with topotecan (at a dose of 1.5 mg/m² per day × 5 days on this trial) were unable to receive an adequate number of courses or individual cumulative dose levels of carboplatin were inadequate to achieve maximal clinical benefit from the platinum agent in contrast to patients completing the less myelosuppressive liposomal doxorubicin, this factor might have contributed substantially to the unfavorable overall survival outcome observed in the topotecan treatment arm. Again, while completely speculative, this hypothesis is quite plausible.

The purpose of this discussion absolutely is not to negate the unquestioned, demonstrated usefulness of topotecan as second-line therapy in ovarian cancer, but rather to point out that the FDA-approved dose level of 1.5 mg/m² per day × 5 days can cause substantial and highly clinically relevant bone marrow toxicity. Whether this toxicity, which can result in a level of fatigue that may cause responding patients to discontinue treatment, should simply be labeled “excessive” rather than “cumulative” appears to be a matter of semantics rather than an important distinction.

Phase II trial data (to date, no randomized phase III experience has been reported) have shown that a lower dose of topotecan (1 mg/m² per day × 5 days or 1.25 mg/m² per day × 5 days) administered as “second-line” treatment of ovarian cancer results in a similar objective response rate, with less bone marrow suppression, compared with the FDA-approved (1.5 mg/m² per day × 5 days) schedule [4, 5]. Because “second-line treatment” of ovarian cancer is realistically delivered as much to optimize overall quality of life (reduce/eliminate or prevent symptoms of disease without replacing them with the toxicity of therapy) as it is to extend ultimate survival, it is very difficult to see any rational argument against administering a lower dose of this agent in this clinical setting. This statement includes any ongoing or future phase III randomized trials in which topotecan is serving as the “control arm” for a new agent attempting to establish a role for itself in the “second-line” treatment of ovarian cancer [6].

Whether delivery of a lower dose of topotecan (1 mg/m² to 1.25 mg/m² per day × 5 days) will essentially eliminate concern for the development of severe clinically relevant marrow toxicity is uncertain, but the risk will certainly be substantially reduced.
(It is relevant to note here that this exact argument can and should be made for the administration of liposomal doxorubicin when used as second-line treatment of ovarian cancer. The FDA-approved dose of 50 mg/m² delivered every 28 days results in a clearly unacceptable incidence of highly clinically relevant severe skin and mucous membrane toxicity [3]. A dose of 40 mg/m² given every 28 days produces a similar objective response rate as 50 mg/m², with a substantially better side-effect profile [7–9].)

Finally, it is important to comment on the description in the Armstrong et al. [1] paper of the toxicities associated with alternative “second-line chemotherapy” agents used in ovarian cancer. The paper notes that “cisplatin and carboplatin have myelotoxicity that may be cumulative” and that “cumulative liposomal doxorubicin and paclitaxel exposure also lead to increased risk of patient morbidity because of cardiotoxicity and neuropathy, respectively.”

In fact, while such side effects can develop, as can serious toxicities of topotecan, there is considerable reported experience documenting the safety and efficacy associated with repeated and prolonged use of carboplatin [10–12], paclitaxel (Taxol®; Bristol-Myers Squibb) [13–15], and liposomal doxorubicin [16], making these agents equally reasonable choices (in addition to topotecan) to be used in the setting of “extended second-line treatment” of ovarian cancer [17].

**Disclosure of Potential Conflicts of Interest**
The author indicates no potential conflicts of interest.

**REFERENCES**


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