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Phase III data on Caelyx® in ovarian cancer

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Abstract

Impressive responses to pegylated liposomal doxorubicin (Doxil/Caelyx®) in pretreated ovarian cancer patients during phase I studies led to a phase II study in platinum and taxane failures. A 26% objective response rate was obtained in this trial and this was confirmed by further phase II studies. The stage was set for a phase III trial in comparison with topotecan, the drug that had become standard in the salvage treatment of patients who were platinum-refractory or -resistant. The completed trial indicates equivalence of results in terms of response rates, time to treatment failure and survival. Differences exist in the toxicity spectrum and in subset analysis according to platinum resistance. On this basis, Caelyx® is being positioned as part of chemotherapeutic regimens in first-line phase III trials.

Keywords: Ovarian cancer; Caelyx; Phase III

1. Introduction

The antitumour activity of pegylated liposomal doxorubicin (Doxil/Caelyx®) in platinum-refractory ovarian cancer has previously been demonstrated in phase II studies performed by a number of workers [1–4]. Based on this promising data, a phase III trial comparing this agent with topotecan in patients previously treated with platinum- and taxane-based chemotherapy was initiated. The results of this study were presented at the American Society for Clinical Oncology in New Orleans, May 2000 and published in full this year [5]. This trial leads one to conclude that Caelyx® is a valuable drug in the second- or third-line setting, and must be integrated further in the treatment of epithelial ovarian cancer. Furthermore, based on phase II results and response rate data only from this comparative phase III trial, Caelyx® received US Food and Drug Administration approval in June 1999 for the treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimen.

This article analyses highlights of the phase III trial, and comments on the potential of specific combinations of Caelyx® with cisplatin or topotecan as experimental regimens to be tested in other phase III trials seeking to identify superior first-line and second-line regimens, respectively.

2. Second-line therapy for ovarian cancer

Carboplatin was initially approved for second-line treatment of ovarian cancer based on demonstrable superior survival over etoposide in one study [6,7] and over 5-fluorouracil in another [7]. This often overlooked fact emphasises the important role of retreatment with a platinum when the disease is still considered platinum-sensitive. The three non-platinum chemotherapeutic agents currently approved for use as second-line therapy for patients with advanced ovarian cancer are altretamine, paclitaxel and topotecan. The activity of altretamine as a second-line therapy was highly variable, probably reflecting the heterogeneity of patients entered, and it is unlikely to play a role in platinum-resistant disease [8].

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General response rates with topotecan and paclitaxel are 13–14% in women who are platinum-refractory [9]. However, since most patients now receive paclitaxel as part of a platinum-containing first-line combination regimen, the utility of paclitaxel as a second- or third-line salvage regimen is limited. In the three largest trials to provide appropriate data, response to topotecan was higher in patients who were platinum-sensitive (initially responded to platinum-based therapy and relapsed more than 6 months after treatment) (19.2–29%) than in patients whose disease was platinum resistant (early or interim relapse) or altogether refractory (11.3–13.3%) [9–11].

Several agents approved for the treatment of other cancers are reported in the scientific literature as having activity in recurrent ovarian cancer, including oral etoposide, gemcitabine, ifosfamide, docetaxel and vinorelbine. Some of these studies suggest significant activity in patients who received one prior platinum-based regimen, with response rates between 10 and 30% [12–16]. There are several drawbacks to these small phase II trials, including the fact that heterogeneous populations were studied consisting of platinum-sensitive and -refractory patients. In addition, there are no controlled trial data for any of these agents versus approved salvage regimens (e.g. topotecan) for the treatment of recurrent ovarian cancer.

Consequently, there is a need to define further the treatment and palliation of patients who fail or who are refractory to the current front-line standard of care for ovarian cancer, i.e. platinum/paclitaxel-based chemotherapy.

3. Caelyx® versus topotecan in platinum- and taxane-pretreated ovarian cancer

A pivotal phase III comparative controlled study involved randomisation to Caelyx® or topotecan of patients with advanced epithelial ovarian carcinoma following failure of first-line platinum-based chemotherapy [5]. Patients who entered the trial were prospectively stratified for platinum sensitivity (patients who progressed >6 months after platinum-based chemotherapy; slightly less than half of those enrolled) or resistance (patients who progressed <6 months after platinum-based chemotherapy) and for bulky disease greater or less than 5 cm (slightly more than half of those enrolled). Patients were randomised to receive Caelyx® 50 mg/m^2 every 4 weeks, or topotecan 1.5 mg/m^2/day as a 30-min infusion for 5 consecutive days every 3 weeks.

The trial was begun in 1997 and accrual completed in March 1999, with 481 patients enrolled; 239 patients were randomised to Caelyx® treatment and 235 to topotecan treatment. The primary endpoint was time to progression; secondary endpoints were survival, response rates, response duration and safety.

The median progression-free survivals were virtually identical in both arms: 18.4 and 18.3 weeks for Caelyx® and topotecan, respectively. The corresponding overall median survivals were 53.4 and 51.1 weeks, respectively. When the subsets of platinum-refractory and platinum-sensitive patients were analysed, surprising differences were seen. The median survival of refractory patients favoured topotecan over Caelyx® (37.3 weeks versus 33.4 weeks), but this difference was not significant. However, in the platinum-sensitive subset, Caelyx® treatment was favoured (86.1 weeks versus 63.6 weeks) and this difference was significant ($P=0.012$). Because this is a subset analysis, it must be interpreted with caution. Nevertheless, it opens up the possibility that the two agents, even though yielding overall similar results, may target different populations.

Response rates were in the range expected from phase II trials of these agents, which is not always the case for multicentre trials. The overall objective response rates were 20 and 17% for Caelyx® and topotecan, respectively. If stable disease status is added to the responding patients, both treatments exceeded 50%. With either treatment, complete responses were less than 5%. Objective responses by platinum sensitivity were quite similar for both agents (12.3 and 6.5% in platinum-refractory patients for Caelyx® and topotecan, respectively; 28% in platinum-sensitive patients for both drugs). Moreover, it is likely that stable disease status represents drug efficacy and is contributing to the observed survival.

In this trial, toxicity comparisons between the two agents yielded the anticipated contrasts: severe myelosuppression with topotecan, and mucosal and skin toxicity with Caelyx®. Topotecan required more dose adjustments and dose delays, and in 3 patients, death from sepsis was considered at least in part drug-related. However, 16% of patients on Caelyx® and 12% on topotecan chose to withdraw from the study because of adverse events.

The phase III study described above convincingly places Caelyx® as an attractive drug for patients with relapsed ovarian cancer. Moreover, from this study there is the suggestion that topotecan and Caelyx® target somewhat different patient populations, even if the overall results do not differ significantly.

Our own experience in 52 patients entered into phase I and II trials of Caelyx® at the University of Southern California had an overall response rate of 31% (including 9 with CA125 defined responses) [17]. Adverse factors for outcome (response, time-to-failure and survival) in our studies were bulky disease and baseline haemoglobin for the last two parameters, and these plus number of prior regimens for response. Few patients on our trial were platinum-sensitive.

4. Caelyx® drug combinations for potential phase III studies

Two combinations hold particular promise for future comparative studies against standard therapy for ovarian cancer:

1. Caelyx® + cisplatin in first-line treatment and in platinum-sensitive second-line treatment
2. Caelyx® + topotecan in second-line treatment after initial platinum-based chemotherapy.

We have piloted both of these combinations extensively in phase I trials since 1997. Cisplatin plus Caelyx® has also been piloted by Gabizon's group in Jerusalem, who published their conclusions with respect to ovarian cancer trials jointly with our group [18]. The recommended dose for further study in previously treated patients is Caelyx® 40 mg/m^2 and cisplatin 60–70 mg/m^2. The major toxicity observed is myelosuppression, particularly thrombocytopenia, seen after several doses, which led us to de-escalate after reaching dose levels as high as Caelyx® 50 mg/m^2 and cisplatin 50 mg/m^2 given days 1 and 8 of each cycle. Unexplained renal events were also seen at these higher levels. Others have proposed substituting carboplatin for cisplatin in this combination, but it is likely that problems with thrombocytopenia will be more prominent and dose attenuation of either agent may be required to achieve the usual six cycles of chemotherapy up-front.

The combination of Caelyx® with topotecan has yielded encouraging results in a phase I study. 5 of 9 patients with ovarian cancer continue to be on treatment at 9–27 months, and maintained on Caelyx® or the combination after initially being induced with the combination. The topotecan was given by 14-day continuous infusion, and oral topotecan is now being tested as part of the combination [19]. The activity of this combination should be confirmed in a phase III study in comparison with either of the two drugs given sequentially.

Currently, no combinations for platinum-refractory disease are superior to single agent [20]. By contrast, in platinum-sensitive disease the CAP (cyclophosphamide/doxorubicin/cisplatin) combination was superior to paclitaxel [21]. However, Caelyx® plus topotecan is supported by theoretical and preclinical considerations of dual topoisomerase inhibition, the possible targeting of two different populations, and the lack of neurotoxicity—always a consideration in previously platinum and taxane pretreated patients.

5. A perspective on ongoing and planned front-line phase III studies

Past and current Gynecologic Oncology Group (GOG) studies have addressed issues separately for early stage disease, for advanced stages and favourable initial debulking, and for advanced stages with unfavourable degree (>1 cm) of residual disease. Recently, because the study dealing with this last patient population is addressing the value of interval cytoreduction after initial chemotherapy, the GOG has also had a separate ongoing protocol for stage IV presentations. The major chemotherapy questions in the recent past have been the substitution of paclitaxel for cyclophosphamide in the platinum-based therapy, the equivalence of cisplatin and carboplatin, and the use of cisplatin via the intraperitoneal (i.p.) route. Some of these studies (paclitaxel substitution, equivalence of the platinums, interval cytoreduction) have at times been initiated or had independent confirmation from studies performed by European groups, by the NCI-C (National Cancer Institute of Canada), or by both together.

European groups constituted by the Medical Research Council (MRC), Italy, Scandinavia and Switzerland have recently performed large international trials such as the recently completed ICON-3. This trial and one of the GOG trials (GOG132) comparing single agent paclitaxel, single agent cisplatin and the combination emphasise the key role of the platinums over the other drugs.

With the availability of several new drugs with activity in second-line therapy and the solid foundation of the platinums in this disease, the next generation of studies will require large numbers of patients if more than one new agent is to be tested. Accordingly, plans are underway for a large international trial including GOG and European investigators to test several arms including two triplets and two sequential doublets, with the proposed standard arm being carboplatin plus paclitaxel. Doxil/paclitaxel/carboplatin is one of the triplets to be included in this trial, whereas gemcitabine appears as part of a triplet and as a sequential doublet, and topotecan only as a sequential doublet, all combined with carboplatin, prior to the paclitaxel/carboplatin doublet (M. Bookman, data not shown).

6. Conclusion

A phase III trial has now confirmed the expected activity of Caelyx® in patients with recurrent ovarian cancer. Not addressed is whether this activity is equivalent or superior to 'free' doxorubicin, or its epi-isomer, epirubicin. Although doxorubicin has been thought to contribute to first-line treatment, it was deemed too toxic and ineffective in the salvage setting [22]. However, epirubicin has shown some activity alone and in combination [23,24]. Nevertheless, randomised studies suggest epirubicin does not add sufficiently to the activity of paclitaxel in the salvage setting [21]. Therefore, it

is unlikely that interest in the 'free' drug will lead to subsequent phase III trials. On the other hand, Caelyx® is expected to be tested up-front in combinations with platinums and in the salvage setting in combination with topotecan. It is unlikely that this last agent will combine as easily with the free anthracyclines or other drugs, as it has with Caelyx®.

As a result of its performance in second-line therapy phase III studies and its toxicity spectrum, Caelyx® is being positioned for combination regimens in up-front phase III studies to be compared with carboplatin plus paclitaxel, the current standard. A number of drug combinations are being tested, but the most likely to be carried forward for such a comparison is the Caelyx® plus carboplatin combination, or a triplet including Caelyx® with carboplatin plus paclitaxel. This triplet is, in fact, an arm of the current Gynecologic Oncology Group 5-arm up-front trial for stages III and IV epithelial ovarian cancer, which has become active in 2001.

References

1. Muggia FM, Hainsworth JD, Jeffers S, *et al*. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol* 1997, **15**, 987–993.
2. Rose P, Gordon AN, Granai CO, *et al*. Interim analysis of a non-comparative multicenter study of Doxil/Caelyx in the treatment of patients with refractory ovarian cancer. *Proc Am Soc Clin Oncol* 1999, **18**, 360a (abstr 1392).
3. Hensley M, Hoppe B, Leon L, *et al*. Clinical use of liposomal doxorubicin in platinum-refractory ovarian cancer: predictors of response in pre-treated patients. *Proc Am Soc Clin Oncol* 2000, **19**, 393a (abstr 1555).
4. Campos SM, Penson RT, MacNeill KM, *et al*. A retrospective analysis of the clinical utility of Doxil in recurrent ovarian cancer. *J Clin Oncol* 1999, **18**, 371a (abstr 1434).
5. Gordon AN, Fleagle JT, Guthrie D, Parkin, Gore ME. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2001, **19** (in press).
6. Kavanagh JJ, Morris M, Smaldone L, *et al*. A randomized trial of carboplatin versus variably timed continuous infusion etoposide (VP16) in refractory epithelial ovarian cancer. *Proc Am Soc Clin Oncol* 1989, **8**, 163.
7. Kavanagh JJ. Carboplatin in refractory epithelial ovarian cancer. In Bunn Jr. PA, Canetta R, Ozols RF, Rozencweig M, eds. *Carboplatin (JM8): Current Perspectives and Future Directions*. Philadelphia, WB Saunders, 1988, 141–146.
8. Muggia FM. Hexamethylmelamine in platinum-resistant ovarian cancer: how active (Editorial). *Gyn Oncol* 1992, **47**, 279–282.
9. ten Bokkel Huinink W, Gore M, Carmichael J, *et al*. Topotecan versus paclitaxel for the treatment of advanced epithelial ovarian cancer. *J Clin Oncol* 1997, **15**, 2183–2193.
10. Creemers GJ, Bolis G, Gore M, *et al*. Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: results of a large European phase II study. *J Clin Oncol* 1996, **14**, 3056–3061.
11. Bookman MA, Malmström H, Bolis G, *et al*. Randomized phase III study of two schedules of topotecan in previously treated patients with ovarian cancer: a National Cancer Institute of Canada Clinical trials Group Study. *J Clin Oncol* 1998, **16**, 2233–2237.
12. Rose P, Blessing J, Mayer A, *et al*. Prolonged oral etoposide as second-line therapy for platinum resistant (PLATR) and platinum sensitive (PLATS) ovarian carcinoma: a gynaecologic oncology group study. *Proc Am Soc Clin Oncol* 1996, **15**, A762.
13. Shapiro JD, Millward MJ, Rischin D, *et al*. Activity of gemcitabine in patients with advanced ovarian cancer: responses seen following platinum and paclitaxel. *Gynecol Oncol* 1996, **63**, 89–93.
14. Markman M, Hakes T, Reichman B, *et al*. Ifosfamide and Mesna in previously treated advanced epithelial ovarian cancer: activity in platinum resistant disease. *J Clin Oncol* 1992, **10**, 243–248.
15. Francis P, Schneider J, Hann L, *et al*. Phase II trial of docetaxel in patients with platinum-refractory advanced ovarian cancer. *J Clin Oncol* 1994, **12**, 2301–2308.
16. Bajetta E, Di Leo A, Biganzoli L, *et al*. Phase II trials of docetaxel; (Taxotere) in advanced ovarian cancer—an updated overview. *Eur J Cancer* 1997, **33**, 2167–2170.
17. Safra T, Groshen S, Jeffers S, *et al*. Treatment of patients with ovarian carcinoma with pegylated liposomal doxorubicin. *Cancer* 2001, **91**, 90–100.
18. Klein P, Hamilton A, Lyass O, *et al*. Phase I studies of Doxil combined with cisplatin: efficacy in epithelial ovarian (Eoc) and Fallopian tube (Ftc) cancers. *J Clin Oncol* 2000, **19**, 410a.
19. Hamilton A, Hochster H, Rosenthal M, *et al*. Continuous infusion topotecan with Doxil: a phase I study of dual topoisomerase inhibition. *J Clin Oncol* 2000, **19**, 200a.
20. Torri V, Floriani I, Tinazzi A, *et al*. Randomized trial comparing paclitaxel + doxorubicin (AIT) versus paclitaxel (T) as second line therapy for advanced ovarian cancer patients in early progression after platinum based chemotherapy. *J Clin Oncol* 2000, **19**, 381a.
21. Colombo N, Marzola M, Parma G, *et al*. Paclitaxel vs. CAP (cyclophosphamide, adriamycin, cisplatin) in recurrent platinum sensitive ovarian cancer: a randomised phase II study. *J Clin Oncol* 1997, **15**, 279.
22. Garcia A, Muggia FM. Activity of anthracyclines in refractory ovarian cancer: recent experience and review. *Cancer Invest* 1997, **15**, 329–334.
23. Vermorkern JB, Koblerska A, van der Burg MEL, *et al*. High dose epirubicin in platinum-pretreated patients with ovarian carcinoma: the EORTC-GCCG experience. *Eur J Gyn Oncol* 1995, **16**, 433–4389.
24. Pfisterer J, Weber B, du Bois A, *et al*. Epirubicin/paclitaxel/carboplatin vs. paclitaxel/carboplatin as first-line treatment in ovarian cancer: results of a safety interim analysis of the AGO-GINECO Intergroup trial. *J Clin Oncol* 1999, **18**, 367a (abstr 1418).