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Caelyx®: phase II studies in ovarian cancer

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Abstract

While there have been significant advances in first-line chemotherapy for advanced ovarian cancer, most patients still relapse with drug-resistant disease. For patients refractory to the two most active agents (platinum and paclitaxel), there are few salvage regimens that possess significant clinical activity together with minimal treatment-related toxicities. Caelyx® is a new treatment for advanced ovarian cancer, which delivers doxorubicin encapsulated in long-circulating Stealth® liposomes, resulting in a prolonged circulation and enhanced tumour targeting of the drug, together with a markedly different safety profile compared with native doxorubicin. Recent phase II clinical trials in relapsed ovarian cancer have demonstrated efficacy in patients with platinum-refractory disease (defined as progression on or relapse within 6 months of previous therapy). In those with combined platinum/paclitaxel-refractory disease, the response rate was 14.5% (95% Confidence Interval (CI): 7.8–21.4%), with many patients demonstrating a prolonged duration of response of beyond 6 months. The most frequent severe (grade 3/4) toxicity with Caelyx® was palmar-plantar erythrodysesthesia (PPE), which occurred in 25% of patients and was managed by dose modification or lengthening the treatment cycle. The incidence of neutropenia and alopecia was much reduced, and the cardiac safety profile was also improved compared with equivalent cumulative anthracycline doses for native doxorubicin. In summary, the evidence of clinical efficacy in patients with platinum-refractory ovarian cancer together with an improved safety profile are all strongly supportive of a positive benefit-risk profile for Caelyx® in the treatment of advanced ovarian cancer following failure of first-line platinum-based therapy

Keywords: Ovarian cancer; Caelyx; Chemotherapy; Platinum-refractory

1. Introduction

Ovarian cancer is the second most common gynaecological cancer and causes more deaths than any other cancer of the female reproductive system. An estimated 25 200 new cases of ovarian cancer are diagnosed annually in the US, and approximately 14 500 women die each year from the disease [1]. Despite improvements in therapy, 55–75% of women who respond to first-line platinum/paclitaxel-based chemotherapy will relapse within 2 years. Of these, there are a subset of patients who will relapse within 6 months of their therapy. Patients who progress while on first-line chemotherapy, or relapse within 6 months of receiving therapy are defined as 'refractory' [2]. Patients who are refractory to both platinum and paclitaxel exhibit characteristic unresponsiveness to currently available 'salvage' chemotherapy.

Three chemotherapy agents are utilised and approved as second-line therapies for patients with advanced ovarian carcinoma: paclitaxel [3], altretamine [4] and topotecan [5]. With increasing integration of paclitaxel into first-line platinum-containing regimens [6,7], it is now used less often as a treatment for recurrent disease. In addition, there are several other cytotoxic drugs that have been reported in the scientific literature as having some activity in recurrent ovarian cancer, albeit in small single centre phase II studies, including oral etoposide [8] and gemcitabine [9]. Thus, while these drugs have demonstrated some efficacy after failure of first-line chemotherapy, each is associated with certain toxicities (i.e. alopecia, myelosuppression) and there remains a need for an active and well-tolerated drug that demonstrates both non-cross resistance together with an acceptable safety profile.

The anthracyclines (e.g. doxorubicin) have a broad spectrum of cytotoxic activity in solid cancers, including

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ovarian cancer. Several early trials demonstrated an overall response rate of 17% in relapsed disease [10], and at least two meta-analyses have shown a small improvement in survival for the addition of anthracyclines to platinum-based first-line therapy [11,12]. In addition to myelosuppression and alopecia, side-effects of anthracyclines include cardiotoxicity due to binding of the molecule to cardiolipin in heart muscle, with the subsequent production of free radicals. The cardiotoxicity is cumulative and limits the dose of doxorubicin that a patient can tolerate during his/her lifetime to 550 mg/m^2. Epirubicin, daunorubicin, carminomycin and doxorubucinol have all been produced through molecular modifications to the anthracycline skeleton in an attempt to improve the safety profile, although they are still associated with the problem of cardiotoxicity to some extent. An alternative approach has been to encapsulate the molecule in a long-acting tumour-selective liposome.

2. Development of Caelyx®

Liposomal encapsulation of doxorubicin significantly alters the pharmacokinetics of the drug, substantially increasing the plasma concentration area under the curve (AUC) compared with conventional doxorubicin [13]. In addition, the structure of the liposomes can be manipulated, providing the capability of altering the spectrum of drug release rates. For example, selection of highly unsaturated fatty acids for use as the phospholipid component increases the rate of release, whereas saturated fatty acids and cholesterol slow the release.

Caelyx® consists of doxorubicin hydrochloride encapsulated in the Stealth® liposome, which contains the phospholipid, hydrogenated soybean phosphatidylcholine. Cholesterol and alpha-tocopherol are added to stabilise the lipid membrane, thus preventing drug leakage, and to serve as an antioxidant to increase product stability, respectively. The surface of the liposome is coated with polymers of methoxypolyethylene glycol (MPEG) in a process referred to as pegylation (Fig. 1). The MPEG polymer molecules impede the attachment of cellular proteins to the liposome surface, protecting the Stealth® liposome from detection by the macrophages of the spleen and reticuloendothelial system. This particular modification to the liposome markedly reduces the plasma clearance of Caelyx®, resulting in prolonged and sustained serum levels [14].

Stealth® liposomes are relatively small, with an average diameter of approximately 100 nm. This size optimally balances the drug-carrying capacity and circulation time, and also permits extravasation through endothelial gaps in the capillary bed of target tumours [15]. The precise mechanism by which Stealth® liposomes enter tumours and release the drug is not completely understood. However, it is believed that these particles circulate for a sufficient period, but are small enough to extravasate through defects or gaps in the capillaries supplying the tumours [16]. Kaposi's sarcoma tumours, in particular, have an inherently leaky capillary bed due to the open-ended or highly permeable (fenestrated) vessels that occur during tumour angiogenesis [17].

After extravasation, it is considered that the Stealth® liposomes lodge in the interstitial spaces among the tumour cells, where they eventually release the encapsulated doxorubicin. A number of possible mechanisms of release have been studied [18]. Liposomes may attach to the cellular surface and the contents slowly diffuse through the liposomal membrane and then through the cellular membrane into the cytoplasm in a process termed absorption. Endocytosis of the liposome is also feasible, with the liposome being degraded and releasing its contents intracellularly. Another option is lipid exchange between the lipids of the liposome and the cellular membrane, during which the contents are passed into the cell. As a consequence of the accumulation and slow release of the drug within the tumour cell

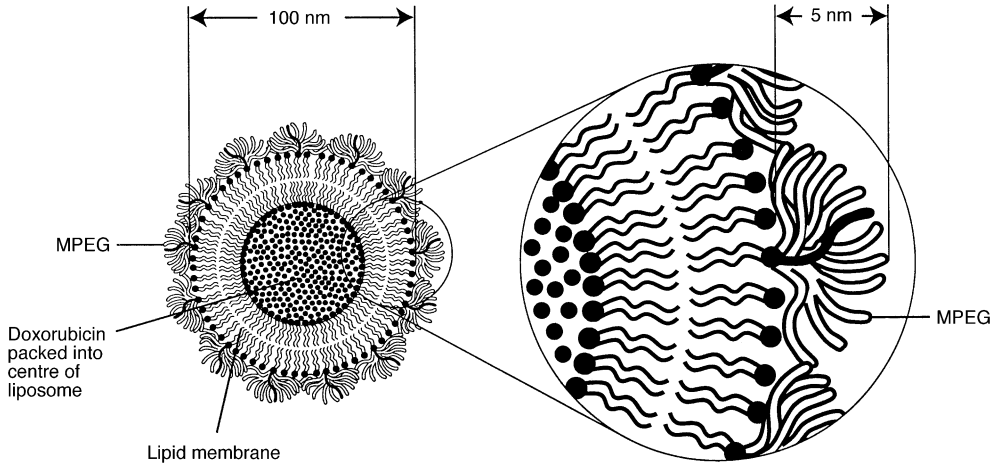

Fig. 1. The Stealth® liposome with methoxypolyethylene glycol (MPEG) outer layer (figure showing the different layers of the liposome).

environment, high levels of free drug can be achieved selectively within malignant cells. Studies in tumour-bearing mice have shown that following treatment with Caelyx®, doxorubicin concentrations achieved in tumours are much higher than in animals receiving comparable doses of unencapsulated free doxorubicin, and, as such, that antitumour activity is greatly enhanced [19–21]. Likewise, much greater accumulation of doxorubicin in tumours has been demonstrated in biopsy specimens of Kaposi's sarcoma that had been treated with Caelyx® compared with normal adjacent skin, confirming the degree of tumour targeting obtained with liposome delivery [22].

In addition to increasing doxorubicin localisation in tumour tissues, the encapsulation of doxorubicin in Stealth® liposomes may result in reduced cardiotoxicity. At least two factors may be involved in this effect. Firstly, a change in tissue distribution with reduced exposure to the drug of sensitive organs, such as the gut, kidneys and heart muscle and, secondly, a slow release of drug, avoiding high peak plasma concentrations of free drug after bolus injection caused by high cumulative doses of doxorubicin. A reduction in cardiotoxicity was observed in dogs after a multiple dose treatment with Caelyx® when compared with an equal dose of free doxorubicin [23]. The reduced toxicity of Caelyx® allows escalation of single and cumulative doses, which could translate into a net gain in therapeutic index if no loss of antitumour activity occurs.

The two main characteristics of Caelyx®, therefore, are that the Stealth® liposomes result in an altered pharmacokinetic profile associated with prolonged circulation due to the volume of distribution being limited to the vascular compartment [24]. As such, the clearance of the drug is markedly reduced, allowing both sustained serum levels and reduced exposure in certain tissues, especially the heart. Secondly, the ability of Stealth® liposomes to extravasate through leaky tumour vasculature allows targeted delivery of Caelyx® to tumours, with release and enhanced accumulation of doxorubicin within the tumour cell environment. These features provide the potential for enhanced delivery of the drug to the tumour together with a markedly different safety profile compared with native doxorubicin.

3. Clinical efficacy of Caelyx® in ovarian cancer

The goal of second-line therapy in ovarian cancer is generally palliative and requires an active agent with a mild toxicity profile to maintain an acceptable quality of life [25]. The rationale for using Caelyx® in ovarian cancer is its superior safety profile as evidenced by a lower incidence of nausea, vomiting and alopecia already seen in previous clinical studies in Kaposi's sarcoma, together with the potential for increased tumour response as a consequence of enhanced delivery to highly angiogenic tumours [24,26]. In addition, during the initial phase I trial, an 8-month partial response was seen in a patient with advanced ovarian cancer that had been unresponsive to several previous different chemotherapy regimens [27].

Three open label, non-comparative phase II studies have been conducted on Caelyx® in a total of 219 patients with ovarian cancer who were refractory to chemotherapy. Studies 30-22 [28] and 30-47 [29] were conducted in the US, while Study 30-47E was conducted in Europe. Patient demographics for the three studies

Table 1
Summary of patient demographics in the three Phase II studies in refractory ovarian cancer

	Study 30-22 [28] ($n=35$)	Study 30-47 [29] ($n=89$)	Study 30-47E ($n=62$)
Age at diagnosis (years)			
Median (range)	63.5 (46–75)	61.0 (34–85)	53.0 (22–80)
Drug-free interval (months)			
Median (range)	1.85 (0.5–15.6)	1.6 (0.6–9.2)	2.6 (0.7–15.2)
Sum of lesions at baseline (cm^2)			
Median (range)	30.5 (1.2–230)	24.4 (0–285)	21.75 (0.3–114)
FIGO staging			
I	1 (2.9%)	5 (5.7%)	6 (9.7%)
II	3 (8.6%)	6 (6.6%)	2 (3.2%)
III	21 (60.0%)	60 (67.2%)	55 (71.0%)
IV	10 (28.5%)	18 (20.5%)	9 (14.5%)
CA-125 at baseline			
Median (range)	131 (20–14,012)	290.25 (7–46,594)	680 (7–31,990)
Number of prior chemotherapy regimens			
1	7 (25.0%)	13 (14.6%)	10 (16.1%)
2	11 (39.3%)	47 (52.8%)	41 (66.1%)
3	6 (21.4%)	29 (32.6%)	11 (17.7%)
4+	4 (14.3%)	–	–

FIGO, International Federation of Gynecology and Obstetrics.

are outlined in Table 1. Studies 30-47 and 30-47E were amended to include patients who were specifically refractory to both platinum and paclitaxel. The dosing regimen was similar for all three studies; Studies 30-47 and 30-47E involved a 50 mg/m^2 dose of Caelyx® on a 4-week dosing interval, while study 30-22 involved the same dose, but initially on a 3-week dosing interval. However, due to protocol-specified dosing delays with this latter study, the actual dosing interval increased to slightly over 4 weeks (median 30 days) [28]. The three protocols employed similar study procedures and, in particular, consistent definitions for evaluating tumour response, all of which underwent independent radiological review. The primary efficacy parameter in all three studies was response rate in the intent-to-treat (ITT) population, i.e. all patients who received at least one dose of the study drug (complete or partial dose). Secondary efficacy parameters included time to response, duration of response and time to disease progression.

3.1. Phase II studies: efficacy endpoints

In the first US study (30-22) in which 35 patients were treated, there was one complete response (CR) and six partial responses (PR), giving an overall response rate for the intent-to-treat population of 20% (95% Confidence Interval (CI): 7–33%). The majority of patients (28/35) were refractory to both platinum and paclitaxel, and the median duration of response was 427 days (range 133–469 days). Of the responders, the majority had a less than 3-month interval since relapsing/progressing from their previous therapy [28]. Overall, the median time to disease progression in this study was 24.6 weeks.

In the second larger 30-47 study, which has been published recently, 89 patients were treated with Caelyx®, 82 of whom were refractory to both platinum and paclitaxel, defined as progression on chemotherapy or within 6 months of completion [29]. Efficacy data from this study are summarised in Table 2. As can be seen, within the platinum/paclitaxel refractory group, 15 patients responded to Caelyx® therapy, including one CR and 14 PRs with a median duration of response of 24.1 weeks, giving an overall response rate of 18.3% (95% CI: 9.9–26.7%). The authors examined the relationship between response and treatment-free interval in these 15 responding patients. They found that the response rate to Caelyx® in patients who progressed while on treatment (platinum and/or paclitaxel) was 15% (6/40 patients), for those who progressed at less than 3 months it was 17.6% (3/17 patients), while for those who progressed between 3 and 6 months after platinum and/or paclitaxel therapy the rate was 24% (6/25 patients). There were 33 patients who had also failed topotecan as second-line therapy, and in these, six responded to Caelyx® including the complete responder (response rate for triple refractory group 18.2%). The overall median time to progression in the ITT population was 19.3 weeks. In addition, there were 36 assessable patients who were classified as having stable disease as their best response. These patients had long periods of treatment before documentation of progressive disease, with a median of 21.9 weeks of therapy [29].

In the 30-47E study conducted in Europe, a total of 62 patients were enrolled, 32 of whom were refractory to both platinum and paclitaxel, and 10 were refractory to platinum, paclitaxel and topotecan. Three out of 20 (15%) platinum-sensitive and one patient refractory to platinum and paclitaxel had a PR to Caelyx®. The overall response rate of 6.5% (4/62 patients) in the study 30-47E was somewhat lower than that recorded in the parallel US study 30-47, even though superficially there appeared to be no significant differences between the demographic profile of the two study groups (Table 1). However, closer analyses showed that more patients in the US 30-47 study had received paclitaxel combined with platinum as their first-line therapy than in the European 30-47E study (75% versus 40%). In contrast, paclitaxel was received more frequently (60% versus 25%) as second- and third-line therapy in Europe (study 30-47E) compared with the US (study 30-47). It has been recognised that the introduction of paclitaxel as first-line therapy has a significant impact on overall survival in ovarian cancer [6,7]. Consequently, these differences may explain the poorer response rate and overall survival seen in the European study population compared with the other US studies.

Table 2
Primary and secondary clinical efficacy data from study 30-47 [29]

Parameter	Platinum/paclitaxel refractory patients	ITT population
No. patients	82	89
Response		
Complete response	1	1
Partial response	14	14
Stable disease	31	36
Progression	18	19
Objective response rate (95% CI)	18.3% (9.9–26.7)	16.9% (9.1–24.6)
Time to response (weeks)		
No. patients	15	
Median (range)	15.1 (3.3–32.9)	
Duration of response (weeks)		
No. patients	15	
Median (range)	24.1 (4.6–48.3)	
Time to progression (weeks)		
Median (range)	17 (0.7–71.6)	19.3 (0.7–86)

ITT, intent-to-treat; 95% CI, 95% Confidence Interval.
19 patients failed to have an evaluation for response.

3.2. Platinum-refractory patients

Patients who are refractory to platinum-based chemotherapy for ovarian cancer and progress during or within 6 months of completing first-line treatment have a poor prognosis and a low likelihood of response to further chemotherapies. A summary of the data for response in all the patients treated in the three Phase II studies, together with those involved in an extension study to 30-22 [30] is given in Table 3. In particular, Caelyx® seems to retain significant clinical activity in this difficult refractory group. Thus for those who progressed on treatment or within 3 months of completing previous platinum-based chemotherapy, the response rates to Caelyx® were 11.1 and 9.3%, respectively (Table 3). Patients whose disease progressed 3 months or more, but less than or equal to 6 months after completing chemotherapy had a response rate of 14.7% (95% CI: 7–22%), which was similar to the platinum-sensitive patients progressing after more than 6 months who had a response rate of 18.5%. In patients refractory to both platinum and paclitaxel ($n = 110$), the response rate was 14.5% (95% Cl 8–21%). In the randomised trial of paclitaxel versus topotecan, the response rates in platinum-refractory patients (interval < 6 months since prior therapy) were 6 and 12%, respectively [31]. Thus, as the majority of patients now received paclitaxel in the first-line setting, the comparator in terms of phase III clinical efficacy trials of Caelyx® for these refractory patients was chosen as topotecan. The results of this prospective study in over 400 patients are discussed elsewhere in this issue by Muggia and Hamilton.

4. Clinical safety of Caelyx®

The five most common adverse events reported during the three phase II studies were palmar-plantar erythrodysesthesia (PPE), asthenia, stomatitis and leucopenia/neutropenia [28,29]. The most common adverse event resulting in dose modification was PPE, which was primarily managed by dose reduction and increasing cycle duration. In the first phase II study, the initial schedule was Caelyx® 50 mg/m^2 every 3 weeks, but of the 19 patients who remained on study at cycle 4 with this schedule, all but one patient had their cycle time increased to either 4 weeks (16 patients) or 5 weeks (2 patients), predominantly due to PPE [28]. As a consequence of this, the median cycle length of the 30-22 study was 30 days, and in addition, 12 of the 21 patients who received more than three cycles of treatment required dose reductions to 40 mg/m^2. As such, the mean dose per cycle was 46.3 mg/m^2. Therefore, the subsequent phase II studies utilised a dose of Caelyx® 50 mg/m^2 on a 4-week schedule with a view to reducing the incidence of moderate to severe PPE.

In study 30-47, the drug-related events occurring with a frequency of 10% or more are shown in Table 4. Only 3 patients withdrew from the study because of PPE (29), and the overall incidence of severe (grade 3/4) PPE was 18%, which was much lower than that observed with the 3-weekly schedule administered in study 30-22. The major dose-limiting toxicities were PPE and haematological toxicity, but both of these toxicities were mild and generally managed by increasing the dosing interval and/or reducing the dose. Some skin toxicity extending beyond the palmar-plantar regions was noted in some patients manifested as a mild rash. Stomatitis was also seen, and was classed as severe (grade 3/4) in 8 patients, one of whom discontinued therapy. Nausea was relatively common in this patient group (61%), but less than two-thirds of these events were thought to be drug-related. There were no reports of total alopecia, and mild hair thinning was only seen in 8 patients (9%). 3 patients had asymptomatic decline in cardiac function manifest by reduction ($> 20\%$) in left ventricular ejection fraction and only 1 patient aged 86 years had clinical symptoms and signs of congestive heart failure and withdrew from the study. Overall, the incidence of cardiac toxicity was markedly less than expected at comparable doses of free doxorubicin.

Table 3
Summary of efficacy of Caelyx™ in platinum-refractory patients as a function of time from platinum failure: combined ITT populations from studies 30-22, 30-47 and 30-47E and extension to studies [28,29,30]

	PD on platinum therapy	PD <3 months after platinum therapy	PD $\geqslant 3$ and $\leqslant 6$ months after platinum therapy	PD >6 months after platinum therapy	Total ITT population
No. patients	9	108	75	27	219
Objective response	1 (11.1%)	10 (9.3%)	11 (14.7%)	5 (18.5%)	27 (12.3%)
Complete response	0	0	2 (2.7%)	0	2 (0.9%)
Partial response	1 (11.1%)	10 (9.3%)	9 (12.0%)	5 (18.5%)	25 (11.4%)
Median time to response (range) (days)	180	96 (23–230)	126 (51–230)	87 (53–197)	113 (23–230)
Median duration of response (range) (days)	427	133 (45–487)	245 (54–469)	134 (68–359)	169 (45–487)
Median time to progression (range) (days)	181 (19–606)	78 (1–795)	100 (5–635)	151 (22–680)	103 (1–795)

PD, progressive disease; ITT, intent-to-treat.

Table 4
Drug-related adverse events in Study 30-47 ($n = 89$) [29]

Adverse event	Drug-related events No. (%)	No. of events			
		Grade 1	Grade 2	Grade 3	Grade 4
Anaemia	35 (39)	9	14	12	0
PPE	37 (42)	9	10	18	0
Neutropenia	33 (37)	11	8	10	4
Nausea	34 (38)	25	3	6	0
Asthenia	37 (42)	20	9	8	0
Stomatitis	31 (35)	11	12	6	2
Rash	25 (28)	11	11	2	1
Mucositis	19 (21)	5	9	5	0
Vomiting	17 (19)	11	2	4	0
Anorexia	12(13)	6	4	2	0
Diarrhoea	11 (12)	8	1	2	0
Thrombocytopenia	8 (9)	6	0	1	1

PPE, palmar-plantar erythrodysesthesia.

In study 30-47E, the common adverse events associated with Caelyx® (i.e. nausea, PPE, stomatitis, asthenia, myelosuppression and rash) were predictable and managed by dose adjustments or delays. PPE led to study discontinuation in 2 patients, and 1 other patient withdrew due to an allergic reaction to the infusion. There were no unexpected toxicities experienced by patients and no evidence of drug-related liver or renal toxicity, and no apparent cardiotoxicity associated with cumulative Caelyx® administration.

5. Conclusions

Based on the phase II data reviewed above, it is evident that Caelyx® possesses promising activity in the second-line treatment of ovarian cancer. It is recognised that patients who have failed first-line therapy with platinum/paclitaxel and, in particular, those who are deemed refractory due to relapse within 6 months, have very few therapeutic options. In the palliative setting, there is a need for new agents that are not only active, but which have a favourable toxicity profile. Caelyx® seems to offer that promise due to its Stealth®-like properties, which result in prolonged plasma circulation and reduced doxorubicin-related toxicities. Equally, there is enhanced drug accumulation within tumours due to targeting and extravasation through abnormal tumour vasculature. The clinical data suggest that Caelyx® has a significant level of activity in the difficult refractory population with an overall response rate between 9 and 15% in those who relapsed within 6 months. It is also well tolerated with minimal evidence of myelosuppression, alopecia or cardiac toxicity, which are the normal concerns with native doxorubicin. The specific drug-related toxicities of PPE and stomatitis were, in general, mild (grade 1–2), and were managed by dose-delay and subsequent preventive procedures. Thus Caelyx® may offer a more favourable clinical profile for such patients in comparison with other approved cytotoxic therapies for relapsed ovarian cancer, and a comparison of the activity of Caelyx® with topotecan, the topoisomerase I inhibitor currently used to treat this group of patients, has been undertaken in the randomised phase III trial 30-49 (see article by Muggia and Hamilton).

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