

# Caelyx: treatment for relapsing ovarian cancer

*Stephen RD Johnston, Stan Kaye*

**Although there have been significant improvements in the first-line treatment of ovarian cancer, the options for patients who relapse have been limited. Caelyx is a new treatment using long-circulating liposomes to target delivery of doxorubicin to the tumour. This article reviews the treatment of ovarian cancer and looks at the place of Caelyx as a new second-line treatment option.**

Ovarian cancer causes around 3900 deaths in England and Wales each year, with the majority of these being women over the age of 45 years (Office for National Statistics, 1999). It is the fourth most common cause of female cancer death after breast, lung and large bowel cancer (Office for National Statistics, 1999). Because there are generally no specific symptoms until the disease has spread beyond the ovaries, the cancer is often advanced at diagnosis, and overall prognosis is correspondingly poor. While first-line treatment of advanced ovarian cancer with current chemotherapy regimens including a combination of platinum and paclitaxel gives high response rates, the great majority of women will relapse with the disease, which is ultimately fatal.

### **OVARIAN CANCER: TREATMENT ISSUES**

In the UK, most women diagnosed with ovarian cancer will undergo de-bulking surgery followed by chemotherapy. Radiotherapy is rarely used. The mainstay first-line chemotherapy agent is paclitaxel in combination with a platinum-containing regimen — this practice was reinforced in May 2000 by guidance from the National Institute for Clinical Excellence (NICE). The guidance stated that paclitaxel in combination with cisplatin or carboplatin should be the standard initial treatment for patients with ovarian cancer following surgery (National Institute for Clinical Excellence, 2000). The guidance was based on evidence that the addition of paclitaxel to standard platinum-based therapy led to an estimated gain in median survival of about 10 months (McGuire et al, 1996; Stuart et al, 1998).

The NICE guidance also recommended that relapsed patients who had not previously been exposed to this drug combination should receive it as second-line therapy, although such patients are now seen less often.

Only 15–20% of women whose disease is advanced at diagnosis are alive 5 years later (Christian and Trimble, 1994). The response rates to salvage drugs are modest, and the duration of response is usually short (Christian and Trimble, 1994). Patients who progress within 6 months of completing platinum or paclitaxel combination therapy are generally even less responsive to the traditional second-line therapies (Gordon et al, 2000), which in addition to paclitaxel include topotecan (Bookman et al, 1998) and altretamine (hexamethylmelamine) (Rustin et al, 1997).

Other cytotoxic agents including oral etoposide (Rose et al, 1998), gemcitabine (Shapiro et al, 1996), docetaxel (Kavanagh et al, 1996), oxaliplatin (Sessa et al, 1999), high dose epirubicin (Vermorken et al, 1995) and vinorelbine (Bajetta et al, 1996) have been reported in scientific literature to have some activity in the treatment of recurrent ovarian cancer. Second-line treatment choices have varied greatly depending on trials available and patients' individual circumstances, including geographical considerations.

For some time there has been a major clinical need for new treatments that are not cross-resistant to first-line platinum-based regimens, and are also well-tolerated by patients. As these patients have little chance of a cure, the goal of second-line therapy is generally palliative, and drugs which have good side-effect profiles mean a better quality of life for patients.

**Dr Stephen RD Johnston** is Senior Lecturer and Consultant Medical Oncologist and **Professor Stan Kaye** is Professor of Medical Oncology, Royal Marsden Hospital, London SW3 6JJ

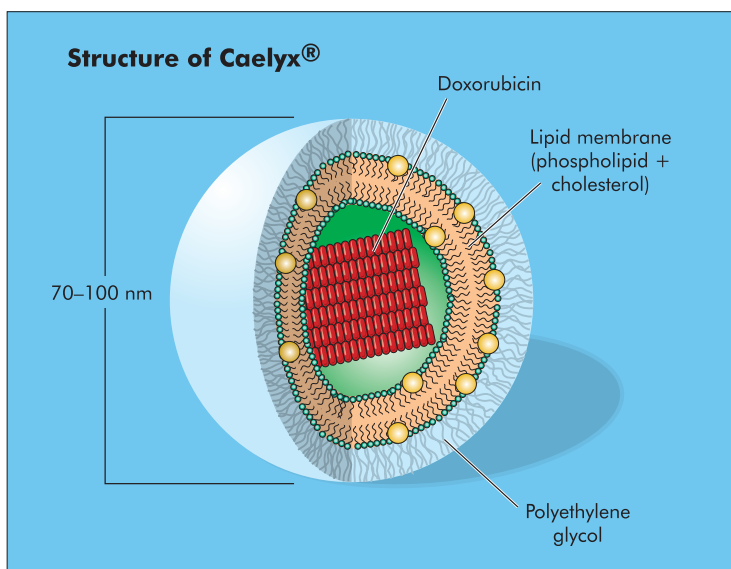
*Correspondence to:*  
*Dr SRD Johnston*

## THE DEVELOPMENT OF CAELYX FOR ADVANCED OVARIAN CANCER

The anthracyclines, including doxorubicin, have demonstrated efficacy in ovarian cancer and other solid tumours. In general, response rates for the anthracyclines doxorubicin and epirubicin as single agents are 30–40% in first-line and 5–20% in second-line treatment (Vermorken et al, 1999). Two meta-analyses have suggested a small improvement in survival for the addition of anthracyclines to platinum-based first-line therapy (Ovarian Cancer Meta-Analysis Project, 1991; A'Hern and Gore, 1995). However, side-effects of these drugs can include severe myelosuppression, alopecia, and accumulative, dose-limiting cardiotoxicity, therefore limiting their usefulness.

Caelyx is a 'stealth' liposome formulation of doxorubicin. The stealth technology involves surface-grafted segments of hydrophobic methoxypolyethylene glycol (MPEG) around the phospholipid coating of each liposome, which helps the liposome evade detection by the immune system (Figure 1). The pharmacokinetics of the drug are characterized by a long circulating half-life, slow plasma clearance, and a reduced volume of distribution compared with conventional doxorubicin or free doxorubicin (Gabizon and Martin, 1997). Cholesterol and alpha-tocopherol are added to stabilize the lipid membrane, which prevents leakage and serves as an antioxidant to increase product stability. Almost 100% of the active drug remains encapsulated in the liposome (Martin, 1997), which helps spare healthy tissue from toxicity, including the heart. The prolonged circulation time and abil-

Figure 1. Structure of Caelyx.



ity of the liposome (which has a diameter of 70–100 nm) to pass through endothelial defects in the tumour microvasculature leads to concentration of doxorubicin in the tumour tissue (Gabizon and Martin, 1997).

Caelyx, marketed by Schering-Plough Ltd, Welwyn Garden City, was approved in the UK in March 1997 for the treatment of acquired immunodeficiency syndrome (AIDS)-related Kaposi's sarcoma, and in November 2000 was launched as a treatment for advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen. In ovarian cancer, it is licensed for intravenous administration at a dose of 50 mg/m<sup>2</sup> once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

Caelyx is characterized by good efficacy and tolerable side-effects — the results of a prolonged circulation time, stability, and a very low rate of detection and removal by the immune system.

## CLINICAL STUDIES

The use of Caelyx in the treatment of advanced ovarian cancer is supported by data from three open label, non-comparative phase II studies and one randomized phase III trial.

### Phase II

The primary efficacy parameter in all three phase II studies was response rate in the intention-to-treat population, and secondary efficacy parameters included time to disease progression and duration of response. Two of the phase II studies were amended to include patients who were specifically refractory to both platinum and paclitaxel.

The initial phase II trial (30-22) (Muggia et al, 1997) was conducted in the USA, and involved 35 patients with recurrent ovarian cancer who had failed to respond to platinum- and paclitaxel-based regimens. Patients received Caelyx monotherapy at a dose of 50 mg/m<sup>2</sup> every 3 weeks. There was an overall response rate of 25.7% (one complete response and eight partial responses), with a median time to progression of 5.7 months, and a median duration of response of 6 months (Table 1).

A second American study (30-47) (Gordon et al, 2000) involved 89 patients with advanced ovarian cancer, 82 of whom were refractory to both platinum and paclitaxel. The patients received Caelyx monotherapy at a dose of 50 mg/m<sup>2</sup> every 28 days. The overall response rate was 16.9% (one complete and 14 partial

responses), with a median time to progression of 19.3 weeks. The median duration of response was 24.1 weeks (Table 2).

The third phase II study (30-47E) (Johnston and Gore, 2001) was a multicentre European study of 62 patients — 32 of whom were refractory to both platinum and paclitaxel, and 11 of whom were refractory to platinum, paclitaxel and topotecan. All patients received Caelyx monotherapy at a dose of 50 mg/m<sup>2</sup> every 28 days. The overall response rate was 6.4% — significantly lower than that recorded in the parallel US 30-47 study. This may be explained by the fact that more patients in the USA study had received paclitaxel and platinum as first-line therapy than in the European study (75% vs 40%) — in the European study, paclitaxel was administered more frequently (60% vs 25%) as second- and third-line therapy. It has been recognized that the introduction of paclitaxel as first-line therapy has a significant impact on overall survival in ovarian cancer (McGuire et al, 1996; Stuart et al, 1998).

The combined response rate data from the three phase II single arm trials and an extension study to 30-22 show that Caelyx seems to have significant activity in patients refractory to platinum-based therapy, and therefore can be an effective salvage therapy in patients failing such a treatment regimen (Johnston and Gore, 2001). For those who progressed during treatment or within 3 months of completing previous platinum-based chemotherapy, the response rates to Caelyx were 11.1% and 9.3% respectively. Patients whose disease progressed more than 3 months but less than 6 months after completing previous platinum-based treatment had a 14.7% response rate. The platinum-sensitive patients who progressed after more than 6 months had a response rate of 18.5%.

### Phase III

A randomized, open-label, comparative phase III study (30-49) (Gordon et al, 2001) supported the results of the phase II trials. The study compared Caelyx with topotecan in 474 advanced ovarian cancer patients who had failed a first-line platinum-containing regimen, with the primary endpoint of time to progression. Secondary endpoints included overall survival, response rate, and safety/toxicity following treatment. A total of 239 patients received Caelyx at a dose of 50 mg/m<sup>2</sup> via a single 1-hour infusion every 28 days, and 235 received topotecan at a dose of 1.5 mg/m<sup>2</sup> via a 30-minute infusion each day for 5 days every 21 days.

Time to progression and overall survival was similar for both groups of patients in the inten-

tion-to-treat population — the median time to progression was 16.1 weeks for the Caelyx group and 17 weeks for the topotecan patients ( $P=0.095$ ), while median overall survival was 60 weeks for the Caelyx patients and 56.7 weeks for the topotecan group ( $P=0.341$ ). The overall response rate was also similar both groups — 19.7% for Caelyx patients, and 17% for topotecan patients ( $P=0.390$ ) (Table 3).

### Platinum-sensitive patients

Patients who relapse or progress more than 6 months after completing treatment are known as 'platinum sensitive', and are generally more likely to respond to further treatment.

The 30-49 study demonstrated significant differences between the Caelyx and topotecan groups. While the response rates were similar (28.4% for Caelyx patients and 28.8% for topotecan patients,  $P=0.964$ ), the median progression-free survival for Caelyx patients was 28.9 weeks, compared with 23.3 weeks for

**TABLE 1.**  
Treatment response for Caelyx in intention-to-treat population: 30-22 phase II study

|                                  |            |
|----------------------------------|------------|
| Overall response                 | 25.7%      |
| Median progression-free survival | 5.7 months |
| Median duration of response      | 6 months   |
| From Muggia et al (1997)         |            |

**TABLE 2.**  
Treatment response for Caelyx in intention-to-treat population: 30-47 phase II study

|                                  |            |
|----------------------------------|------------|
| Overall response                 | 16.9%      |
| Median progression-free survival | 19.3 weeks |
| Median duration of response      | 24.1 weeks |
| From Gordon et al (2000)         |            |

**TABLE 3.**  
Treatment response for the intention-to-treat population: 30-49 phase III study

| Intention-to-treat population                     |                | Caelyx (n=239) | Topotecan (n=235) |
|---|----------------|----------------|-------------------|
| Overall response<br>( $P=0.390$ )                 | Total          | 47 (19.7%)     | 40 (17.0%)        |
|   | Complete       | 9 (3.8%)       | 11 (4.7%)         |
|   | Partial        | 38 (15.9%)     | 29 (12.3%)        |
|   | Stable disease | 77 (32.2%)     | 95 (40.4%)        |
| Median progression-free survival<br>( $P=0.095$ ) |                | 16.1 weeks     | 17.0 weeks        |
| Median survival<br>( $P=0.341$ )                  |                | 60 weeks       | 56.7 weeks        |
| From Gordon et al (2001)                          |                |                |                   |

topotecan patients ( $P=0.037$ ). Median overall survival for Caelyx patients was 108 weeks compared with 71.1 weeks for topotecan patients ( $P=0.008$ ).

Currently, many platinum-sensitive patients are re-challenged with a platinum-based drug as second-line therapy. Caelyx provides a good option for women who have experienced dose-limited myelosuppression or platinum hypersensitivity during first-line treatment.

#### Platinum-refractory patients

Patients who progress during or within 6 months of completing first-line therapy with a platinum-containing regimen are known as 'platinum resistant' or 'platinum refractory', and have a low likelihood of responding to further therapies.

In the phase III study, the overall response rate was 12.3% for Caelyx patients with platinum-resistant tumours, compared with 6.5% for topotecan patients. The difference was not significant ( $P=0.118$ ). There were trends in favour of topotecan for progression-free survival (9.1 weeks for Caelyx patients and 13.6 weeks for topotecan patients,  $P=0.733$ ) and for overall survival (35.6 weeks for Caelyx patients and 41.3 weeks for topotecan patients,  $P=0.455$ ).

#### SAFETY DATA

A good safety profile is important in ensuring that women with advanced ovarian cancer have the best possible quality of life during their treatment.

The most common adverse events reported during the phase II studies were palmar-plantar erythrodysesthesia (PPE, also known as hand-foot syndrome), asthenia, stomatitis and leucopenia or neutropenia (Muggia et al, 1997; Gordon et al, 2000). PPE was the most com-

mon dose-limiting event, which was mainly managed by dose reduction and increasing the length of the cycle.

The phase III study comparing Caelyx with topotecan showed that Caelyx patients experienced fewer and less severe haematological events, nausea and alopecia (Gordon et al, 2001) (Table 4). In the phase III study, treatment-related adverse events (intention-to-treat population) observed with Caelyx again included PPE and stomatitis. PPE was seen in 49% of Caelyx patients (grade 3–4 in 23%), and stomatitis in 40% of patients (severe in 8%). Both the incidence and severity of haematological adverse events were greater with topotecan than with Caelyx. Neutropenia and anaemia were reported in about three-quarters of the topotecan group compared with about 35% with Caelyx. Thrombocytopenia occurred in nearly two thirds of the topotecan group, compared to only 13% with Caelyx. Neutropenia was severe or life-threatening (grade 3 or 4) in 77% of topotecan patients, compared with 12% of Caelyx patients. Anaemia, thrombocytopenia and leucopenia were also reported as grade 3 or 4 adverse events in a larger proportion of topotecan-treated patients. The incidence of alopecia was three times higher in topotecan patients (49% compared with 16% for Caelyx). These results have  $P$  values  $<0.001$  except in the case of grade 3–4 alopecia, where  $P=0.007$ .

Caelyx patients involved in the phase III study required fewer dose modifications than those being treated with topotecan. More patients in the topotecan group needed growth factor support and blood transfusions, which are associated with significant costs. A comparable number of patients (43 Caelyx patients and 37 topotecan) discontinued because of adverse events.

**TABLE 4.**  
Adverse events: 30-49 phase III study

| Adverse event    | Caelyx (n=239) |            | Topotecan (n=235) |            |
|------------------|----------------|------------|-------------------|------------|
|                  | All grades     | Grades 3-4 | All grades        | Grades 3-4 |
| Neutropenia      | 84 (35%)       | 29 (12%)   | 191 (81%)         | 180 (77%)  |
| Anaemia          | 85 (36%)       | 13 (5%)    | 169 (72%)         | 66 (28%)   |
| Thrombocytopenia | 31 (13%)       | 3 (1%)     | 152 (65%)         | 80 (34%)   |
| Leukopenia       | 87 (36%)       | 24 (10%)   | 148 (63%)         | 117 (50%)  |
| Alopecia         | 38 (16%)       | 3 (1%)     | 114 (49%)         | 14 (6%)    |
| PPE              | 117 (49%)      | 55 (23%)   | 2 (1%)            | 0          |
| Stomatitis       | 95 (40%)       | 20 (8%)    | 35 (15%)          | 1 (0.4%)   |

$P<0.001$  for all events except for grade 3–4 alopecia, where  $P=0.007$ . From Gordon et al (2001). PPE = palmar-plantar erythrodysesthesia

### Cardiac safety

The use of anthracyclines such as free doxorubicin in advanced ovarian cancer is limited by cardiotoxicity. Data on the cumulative cardiac tolerability of Caelyx are limited because few patients have received cumulative doses higher than 500 mg/m<sup>2</sup> (Coukell and Spencer, 1997). However, Caelyx appears to be associated with a lower incidence of cardiac toxicity than free doxorubicin.

In a study of Caelyx as a long-term treatment for advanced AIDS-related Kaposi's sarcoma, conducted over 30 months, cardiac toxicity was not seen in any patient. Two patients in this study received cumulative doses of 670 mg/m<sup>2</sup>, and cardiac biopsies of these patients were undertaken to exclude cardiac damage (Szelényi et al, 1992).

The results of an endomyocardial biopsy comparing cardiotoxicity in AIDS-related Kaposi's sarcoma patients treated with Caelyx and free doxorubicin indicate that Caelyx in high cumulative doses is significantly less cardiotoxic than free doxorubicin (Berry et al, 1998).

In its most serious form, cardiac toxicity associated with free doxorubicin consists of a cardiomyopathy that increases in frequency with higher cumulative doses — the high peak plasma level of drug accompanying a standard infusion is believed to be an important factor in this. Liposomal encapsulation of anthracyclines lowers peak plasma concentration, and animal models have shown that this reduces cardiotoxicity (Berry et al, 1998).

### Managing PPE

PPE, which has been reported to occur in about a third of Caelyx patients, can range from a tenderness of the palms and soles to severe blistering, swelling or ulceration that can prevent walking or using the hands. Patients should be advised to carry out preventative measures, such as keeping the hands and feet cool and aired and avoiding exposure to very hot water, for 4–7 days after each infusion.

Clinical experience points to the condition being cumulative, with skin problems generally appearing in about the third cycle of treatment. In most patients, PPE is mild and resolves in 1–2 weeks, meaning prolonged treatment delays are not necessary. However, for patients with severe symptoms, dose modifications may be required. Guidelines for dose modification are included in the drug's summary of product characteristics. Pyridoxine and dimethyl sulfoxide can occasionally provide symptom relief.

### COST EFFECTIVENESS

An economic evaluation of the phase III Caelyx vs topotecan study — from a UK perspective — has concluded that the average total treatment cost is significantly lower with Caelyx than with topotecan (Smith et al, 2001). The study shows the average combined cost of the drug plus the cost of administering the drug (i.e. the cost of the drug plus intravenous services, nursing time and hospital attendance) was similar for both drugs — about £9000 for each drug.

While the actual drug cost of Caelyx is higher than that of topotecan, more frequent administration is required with topotecan (an intravenous infusion daily for five consecutive days every 3 weeks instead of a single infusion every 4 weeks), which makes administration of topotecan much more expensive. But the real difference in cost occurred in management of side effects from the two drugs, mainly because of the higher costs involved with the management of grade 3 and 4 haematological toxicities associated with topotecan. The average cost of managing the side effects of Caelyx was estimated at £800 per patient, compared with about £2800 for topotecan. This means an estimated average total treatment cost of about £9800 per Caelyx patient, compared with £12 000 per topotecan patient.

### PATIENT PROFILE

Caelyx could be suitable for a significant number of women who relapse from first-line treatment. It is particularly well-suited to patients who tolerated first-line treatment poorly because of myelosuppression but may benefit from further treatment. It has significant survival benefit for platinum-sensitive patients, and has also been shown to be effective in platinum-refractory patients. The fact that Caelyx is only administered once every 4 weeks is also an advantage for patients who have to travel a long way for treatment.

### FUTURE USE

There is limited scope for combining anthracyclines, e.g. free doxorubicin, with taxanes because of the high risk of haematological toxicities. However, Caelyx's good side-effect profile means it may be suitable for combination with either paclitaxel or docetaxel, in breast cancer as well as ovarian cancer. Combination trials involving Caelyx are underway in advanced breast cancer and it is also being investigated as combination therapy for ovarian cancer with drugs including paclitaxel, cisplatin, topotecan and gemcitabine. A NICE appraisal of Caelyx as second-line therapy for advanced ovarian cancer is underway, and is due to be completed in May 2002.

## CONCLUSIONS

The rationale for using Caelyx in ovarian cancer is its potential for increased tumour response as a consequence of enhanced delivery to tumours, together with its superior safety profile (Gabizon and Martin, 1997).

Caelyx fills a previously unmet need for women with advanced ovarian cancer. For patients who are resistant to platinum or have had problems with toxicities including myelosuppression, there have been few second-line therapies that have significant efficacy and minimal treatment-related toxicity. Given the fact that most advanced ovarian cancer patients will now have been exposed to paclitaxel/platinum and given the toxicities associated with other licensed second-line treatments, Caelyx is a good option for patients who have failed first-line therapy. **HM**

*Conflict of interest: Dr Johnston and Professor Kaye have sat on advisory boards for Schering-Plough Ltd on the use of Caelyx in ovarian cancer.*

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## KEY POINTS

- The majority of women with advanced ovarian cancer will relapse from first-line treatment.
- There has been a need for new treatments which are effective after first-line platinum-based therapy and are well-tolerated by patients.
- Caelyx, a liposomal formulation of doxorubicin, was launched in the UK in November 2000.
- Caelyx has good efficacy in women who have failed first-line platinum-based chemotherapy, and has an acceptable side-effect profile.
- Caelyx is simple to administer (once every 4 weeks), and offers physicians a good treatment option for patients with relapsed disease.