Pegylated liposomal doxorubicin HCL (PLD; Caelyx/Doxil®): Experience with long-term maintenance in responding patients with recurrent epithelial ovarian cancer

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Background: We hypothesized that a response to pegylated liposomal doxorubicin (PLD, Caelyx/Doxil) followed by maintenance is beneficial and safe in recurrent ovarian cancer.

Patients and methods: Sixteen patients have received PLD for more than 1 year for recurrent ovarian (14) or fallopian tube (2) cancer. All had stable disease or better responses to PLD + carboplatin (5) or topotecan (9) doublets or to PLD alone (2). PLD maintenance therapy 30–40 mg/m2 was given every 4–8 weeks. This analysis focuses on cardiac status, overall tolerance, and time to recurrence.

Results: Termination of PLD was due to progression in all patients. Noteworthy was the lack of cumulative myelosuppression and, with one exception, clinical cardiac toxicity. This patient was hospitalized with cardiogenic shock and fever complicating grade 4 pancytopenia from topotecan ten months after discontinuation of PLD. Seven patients continue to receive PLD after a median of 1680 mg/m2 (1180–2460 mg/m2). Four of these had documented relapses after 3–6 years on maintenance occurring in the setting of lengthening of the treatment interval. Maintenance PLD was re instituted after ‘reinduction’ with a platinum.

Conclusions: PLD appears to be safe as long-term maintenance in ovarian cancer and may be important for a continued response.

Key words: ovarian cancer, maintenance therapy, liposomal doxorubicin

introduction

Despite high overall response rates to ‘induction’ platinum and taxane-based chemotherapy, the majority of patients with advanced ovarian cancer have persistent disease or demonstrate recurrences within 2 years, thereafter becoming candidates for further chemotherapy. A trial evaluating maintenance paclitaxel was stopped early after showing prolongation of progression-free survival when given to patients achieving clinical complete response (CR) after first-line chemotherapy [1]. Updated analyses support a hypothesis of persistent impact from 1-year maintenance that may translate into survival advantage.

Following failure of platinumus and taxanes several cytotoxic agents have shown activity but none were able to induce durable remissions in the absence of continued treatment. Therefore, although secondary treatments have response rates in 14%–40%, these responses are rarely complete and the disease recurs shortly after discontinuation of therapy. When these agents are combined with platinums in patients with platinum-sensitive recurrences, high response rates and long response durations are expected [2–7]. These almost, however, never exceed the initial duration of response [8].

Objective responses and evidence of prolonged stabilization of disease have been achieved with caelyx/doxil with generally tolerable and predictable toxicity in several studies [9–13]. In our initial study of caelyx/doxil, only two CRs were achieved and both patients relapsed 3 months and 11 months following discontinuation. On the other hand, we observed long duration of stable disease with every 4-weeks maintenance in the absence of severe symptoms [14].

Since similar experiences have been reported by others treating acquired immunodeficiency syndrome (AIDS)-related Kaposi’s sarcoma [15–18] and by some treating solid gynecologic cancers [19], we hypothesized that maintenance caelyx/doxil could be safe and could yield prolonged survival in responsive patients. Our first concern was cardiac safety, and before embarking on such strategy we reviewed our experience with caelyx/doxil single-agent repetitive doses in our phase I/II trials. Such analysis demonstrated no cardiac clinical or subclinical problems after 500 mg/m2 in patients not previously treated with anthracyclines [20]. Accordingly, in subsequent
phase I–II doublet protocols of caelyx/doxil combined with cisplatin, topotecan (GlaxoSmithKline, Philadelphia, PA), or carboplatin [21–23] as well as in patients who were started on caelyx/doxil alone off protocol, for platinum-resistant recurrences usually after four cycles of combination chemotherapy or after maximal response we implemented a policy of caelyx/doxil given as maintenance in the absence of progression unless patients opted for discontinuation. In addition to low noncutaneous toxicity, the hypothesis behind such a policy is the desirability of maintaining a critical intratumoral (i.t.) concentration to avoid emergence of resistance from inadequate drug exposure. In this report, we describe the toxicity and outcome of 16 patients with gynecological cancer selected for having exceeded 1 year of maintenance treatment with caelyx/doxil within our clinical trials at a cut-off date of June 2004, to ensure adequate review of patient data.

patients and methods

Patients with relapsed ovarian and fallopian tube carcinomas were included if treated on three Institutional Review Board-approved protocols or with caelyx/doxil alone (within the practice of the principal investigator). Sixteen patients who were continued on caelyx/doxil (Sequus Pharmaceuticals Inc., Menlo Park, CA) for >1 year were identified by June 2004, and the results were updated to July 2006.

eligibility criteria

All patients had histologically documented papillary serous cancers and had undergone initial surgical debulking followed by six cycles of platinum-based chemotherapy up front. Patients had received a median of 1 (range 1–3) previous chemotherapeutic regimens up to the time of recurrence for which they were treated with caelyx/doxil alone or entered in the trials of caelyx/doxil doublets.

treatment and study procedures

Fourteen patients were treated with a maintenance regimen of caelyx/doxil alone (following a doublet of caelyx/doxil + carboplatin in five or caelyx/doxil + topotecan in seven or caelyx/doxil monotherapy in two patients); in two other patients, with exceptional tolerance to the initial doublet of caelyx/doxil + topotecan, maintenance consisted of caelyx/doxil in combination with topotecan as previously published [22] in doses of 0.3–0.4 mg/m²/day for 10–14 days.

Maintenance therapy with caelyx/doxil consisted of 30–40 mg/m² given every 4–8 weeks as a 1-h infusion in 250 cm³ 5% dextrose in water. In the two patients cited above, topotecan was given as a continuous infusion.

Baseline left ventricular ejection fraction (LVEF) determinations were obtained by multiple gated acquisition (MUGA) scans. Cardiac status follow-up was to be obtained during protocol treatment and during maintenance phase every 300 mg/m² (approximately annually) using echocardiogram or MUGA scans and at completion of treatment. Objective responses were defined by standard criteria [24]. Dose adjustments after year 1 were carried out to lengthen the interval by 1 week while maintaining the dose if there were persistent grade 2 skin toxic effects. Once adjusted, patients remained on the same dosing interval unless further lengthening was necessary.

All patients on the protocols had given written informed consent before treatment fulfilling all institutional, state, and federal requirements.

results

A total of 16 patients including 14 with recurrent ovarian cancer and two with fallopian tube carcinomas were identified as receiving >1-year caelyx/doxil at the cut-off date of June 2004.

time on maintenance

Four patients with ovarian cancer received caelyx/doxil maintenance after achieving a CR (including CA 125 normalization): three of them had been treated with caelyx/doxil plus carboplatin (AUC5) as second-line treatment, while the fourth received a caelyx/doxil plus topotecan as second line. The caelyx/doxil cumulative doses ranged from 1360 to 2125 mg/m² and their time on this second-line treatment was 60 months+, 60 months+, 59 months, and 95+ months. Their progression-free intervals (PFIs) after their initial induction were 39, 6, 20, and 12 months (Table 1, patients 5, 12, 8, 7).

Nine patients, seven with ovarian cancer and two with fallopian tube cancer, were placed on maintenance after achieving a partial response (PR): (six after caelyx/doxil plus topotecan, two after caelyx/doxil plus carboplatin, and the ninth had received caelyx/doxil alone). Additionally, three patients with ovarian cancer were placed on maintenance after achieving only disease stabilization: Two after caelyx/doxil plus topotecan and one after caelyx/doxil alone. The cumulative median dose administered for these 12 patients was 935 mg/m² (range 595–2460 mg/m²+). Overall for these patients, the mean (PFI) on caelyx/doxil maintenance was 37 months (range 18–71+) which was longer than the mean PFI of 28.5 months (range 10–45 months) seen with prior therapy. For patients who had been on only one prior regimen, the time on treatment was 64+ months (first PFI, 29 months), 23 months (first PFI, 16 months), 71+ months (first PFI, 10 months), and 18 months (first PFI 29 months). For other patients with PR or stable disease on multiple prior regimens, their time on treatment were; 18 months, 23 months, 55+ months, 29 months, 59 months, 20 months, 33 months, and 34 months.

treatment status

Overall nine patients were removed from caelyx/doxil maintenance because of progression, and none because of toxicity or patient preference. The seven currently still on maintenance caelyx/doxil therapy are shown in Table 1. Noteworthy are late relapses with subsequent response achieved with reintroduction of a platinum compound in combination with caelyx/doxil, this was again followed by caelyx/doxil maintenance as a single agent. Three patients relapsed when intervals of maintenance therapy were lengthened (cases 5, 7, 8) and the fourth after discontinuation of therapy (case 10). In a fifth patient (case 9) carboplatin + caelyx/doxil for 4 doses induced regression of a paraaortic node that continues on caelyx/doxil to date.

toxicity

All patients had minimal signs of skin toxicity consisting of palmar-plantar erythrodysesthesia (PPE). Some patients also experienced mild rashes elsewhere and increased pigmentation.
The interval between doses was increased by 1 week as noted if the grade of toxicity exceeded grade 1. Beyond the second year adjustments were made based on patient convenience, without exceeding an 8 week interval. No patients experienced venous problems, and premedications (antiemetics, steroids) were not required in the maintenance phase.

During the maintenance phase, caelyx/doxil monotherapy was well tolerated with no grade 4 toxicity, two grade 3 neutropenias, and one grade 3 mucositis. Other grade 3 toxic effects, namely hypersensitivity reactions, diarrhea, or infection were observed in one patient each. Toxic effects associated with caelyx/doxil in combination with carboplatin have been previously reported [23]. Of the three patients treated with caelyx/doxil in combination with carboplatin only one had grade 3 thrombocytopenia before the maintenance phase. Patients on the doublet caelyx/doxil/topotecan were included in a prior publication [22]. The two patients receiving the caelyx/doxil + topotecan doublet during the maintenance phase experienced grade 3 and 4 toxic effects consisting of neutropenia and thrombocytopenia.

No confirmed decline in ejection fraction (EF) on a subsequent determination was observed on caelyx/doxil maintenance. One patient, however, experienced 10 months after stopping caelyx/doxil for disease progression, cardiogenic shock (EF 20% recovering to 45%) during neutropenic sepsis complicated by grade 3 diarrhea from recently instituted oral topotecan. Table 2 shows a summary of cardiac assessment results.

**Discussion**

Second-line treatments in patients with relapsed epithelial ovarian cancer provide effective palliation and may extend survival, but relapse is invariably. An effective maintenance therapy that would delay recurrences after a clinical CR or control the progression in partially or minimally responding disease could have a potential impact on survival.

The concept of consolidation and/or maintenance in ovarian cancer after platinum/paclitaxel induction was given impetus by the Southwest Oncology Group/Gynecologic Oncology Group (SWOG/GOG) study demonstrating that 12 cycles of intravenous paclitaxel administered every 28 days after achieving a clinical CR, resulted in a 7-month improvement in median progression-free survival, compared with those who received only three cycles of paclitaxel [1]. An update of this study indicated differences in recurrence were maintained on a subsequent follow-up [25], and subsequent hypothesis-generating analysis raises the possibility that it may have an impact on survival for the subset with the lowest CA 125 nadir at the outset [26, 27].

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**Table 1. Update on patients still receiving doxil/caelyx**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Cumulative dose mg/m²</th>
<th>Current dose schedule</th>
<th>Cardiac evaluation MUGA/Echo</th>
<th>Toxicity/current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>#5</td>
<td>54</td>
<td>1245</td>
<td>40 mg/m², Q6wk in 2004, Q7wk February 2005–October 2005, then Q8wk to 10wk presenting 2006</td>
<td>Echo: 2006 normal cardiac function</td>
<td>Skin (ulcerated heel callus); prolong interval and decrease dose/patient relapsed June 2006, after 55 m in remission with PET/CT pos and CA 125 rise to 71</td>
</tr>
<tr>
<td>#7</td>
<td>68</td>
<td>1360</td>
<td>30 mg/m², Q6wk in 2004–June 2005, but July 2005 Q7wk</td>
<td>MUGA: 2006 normal LVEF 70%</td>
<td>No toxicity but does have hypertension and creatinine 2.0, for which interval was lengthened/rising CA 125, January 2006–18 April 2006: carbo (AUC 4) and doxil 56 mg, 5 cycles</td>
</tr>
<tr>
<td>#8</td>
<td>64</td>
<td>1680</td>
<td>30 mg/m², 2004: Q4wk, January 2005–April 2005; Q5wk, May 2005–December 2005: Q6wk, January 2006: Q7wk</td>
<td>Echo: stress echo May 2006 normal cardiac function</td>
<td>No toxicity but does have hypertension and creatinine 2.0 for which interval recently lengthened July 2003 relapse (rise in CA 125 and pos PET/CT), September 2003–24 November 2003: carbo (AUC 5) and doxil 30/m² × 4 doses. Negative PET/CT</td>
</tr>
<tr>
<td>#15</td>
<td>60</td>
<td>2460</td>
<td>40 mg/m², Q5wk</td>
<td>Coronary stent following episodes of anginal pain; normal ECHO</td>
<td>Grade 1 skin toxicity</td>
</tr>
<tr>
<td>#16</td>
<td>63</td>
<td>2125</td>
<td>30 mg/m², January 2004–June 2006: Q7wk</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MUGA, multiple gated acquisition; Q, every; wk, week; m, month; PET, positron emission tomography; CT, computed tomography; AUC, area under the curve; LVEF, left ventricular ejection fraction.
Table 2. Summary of LVEF results for assessment of cardiotoxicity

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cumulative doxil dose (mg/m²)</th>
<th>EF before Rx⁰ (%)</th>
<th>EF after Rx⁰ (%)</th>
<th>Δ EF (%)</th>
</tr>
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<tbody>
<tr>
<td>#1</td>
<td>490</td>
<td>64</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>#2</td>
<td>560</td>
<td>53</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>#3</td>
<td>760</td>
<td>68</td>
<td>71</td>
<td>+3</td>
</tr>
<tr>
<td>#4</td>
<td>875</td>
<td>74%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>#5</td>
<td>1245</td>
<td>ND</td>
<td>50–70</td>
<td>ND</td>
</tr>
<tr>
<td>#6</td>
<td>770</td>
<td>66</td>
<td>58</td>
<td>–8</td>
</tr>
<tr>
<td>#7</td>
<td>1360</td>
<td>69</td>
<td>70</td>
<td>–4</td>
</tr>
<tr>
<td>#8</td>
<td>1680</td>
<td>68</td>
<td>62</td>
<td>–4</td>
</tr>
<tr>
<td>#9</td>
<td>1850</td>
<td>65</td>
<td>67</td>
<td>+4</td>
</tr>
<tr>
<td>#10</td>
<td>1180</td>
<td>64</td>
<td>70</td>
<td>+6</td>
</tr>
<tr>
<td>#11</td>
<td>1000</td>
<td>ND</td>
<td>61, 64, 20⁵</td>
<td>–4⁴b</td>
</tr>
<tr>
<td>#12</td>
<td>1135</td>
<td>66</td>
<td>50–70</td>
<td>0</td>
</tr>
<tr>
<td>#13</td>
<td>1200</td>
<td>ND⁴</td>
<td>ND⁴</td>
<td>ND⁴</td>
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<tr>
<td>#14</td>
<td>1250</td>
<td>57</td>
<td>50–70</td>
<td>0</td>
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<tr>
<td>#15</td>
<td>2460</td>
<td>74</td>
<td>70</td>
<td>–4</td>
</tr>
<tr>
<td>#16</td>
<td>2125</td>
<td>64</td>
<td>75</td>
<td>+11</td>
</tr>
</tbody>
</table>

⁰Multiple gated acquisition scan unless stated.
⁵This occurred during septic episode from oral topotecan 10 months after doxil in setting of neutropenic sepsis; had recovered to 45% 3 months postseptic episode.
⁴Patient refusal.
⁴EF, ejection fraction; ND, no data.

The concept of maintenance after first recurrence is even more compelling: subsequent responses tend to be shorter than the first disease-free interval [8]. The clinical utility of prolonged maintenance therapy in patients achieving CR to second-line chemotherapy, however, has not been established. A prescribed number of cycles is reasonable for platinum-based treatment because some long durations of response may be anticipated and continuing beyond six cycles with a platinum compound leads to progressive intolerance. Nonplatinum drug regimens, however, should not be subjected to such limitations since they rarely result in CRs, are generally better tolerated, and have no appreciable worsening of toxic effects with repeated cycles [28].

Maintenance chemotherapy may, therefore, be attractive for several second-line drugs. Commonly used second-line drugs such as gemcitabine or topotecan have dose-limiting myelosuppression that is not cumulative. Taxanes are generally well tolerated except for problematic sensory neuropathy, edema, extensive chronic alopecia, and nail changes. Caelyx/doxil maintenance may be particularly advantageous given the long intervals between drug administrations that are further increased when tailored to reduce dermatologic toxicity. Furthermore, fear of clinical cardiac problems is unwarranted if the patient’s medical status is stable [10–13, 18–20, 31] and they have not been exposed to anthracyclines.

Cardiac safety is further supported by histologic assessment of patients with advanced malignancies who received a median caelyx/doxil dose of 708 mg/m² [31]. Data from a series of patients with AIDS-related Kaposi’s sarcoma indicate that some patients may tolerate cumulative caelyx/doxil doses up to 2360 mg/m² given over a 5-year period with little or no decrease in cardiac function [18]. In a study of 509 patients with metastatic breast cancer, some of whom had received adjuvant-free anthracyclines, progression-free survival was similar for both caelyx/doxil and conventional doxorubicin, but the incidence of cardiac toxicity was significantly lower with caelyx/doxil [32] and no events were clinical with this formulation.

Preclinical findings reinforce attractive aspects of caelyx/doxil maintenance. Immunosuppressed mice tolerate this formulation better than the free compound [33, 34]. Passive targeting leads to drug accumulation and continuous exposure of tumors to therapeutic levels over a wide range of doses that may minimize the emergence of resistance [15, 35, 36], and/or inhibit angiogenesis [37–39]. A number of clinical studies have attested not only the activity of this formulation against ovarian cancer, but also have confirmed its safety over many cycles [32, 40]. In the phase III randomized trial versus topotecan, an advantage in survival emerged for caelyx/doxil indicating that response to this agent was associated with greater duration of response and hence survival. In part, this may be attributed either to efficacy of continued treatment or better tolerance to subsequent treatment or both [41].

The current experience documents the feasibility of prolonged caelyx/doxil therapy in patients who achieved CR, PR, or stable disease in recurrent ovarian cancer. With regards to safety, patients on maintenance in this study typically tolerated it with no alopecia, nausea and vomiting, and importantly absence of significant cumulative myelosuppression or grade 4 mucositis. PPE was seldom greater than grade 1 since the interval was progressively adjusted to skin tolerance. The only significant cardiac event occurring 10 months after discontinuation of caelyx/doxil, a 23% decline in EF, was attributed to oral topotecan-induced toxicity leading to septic shock. On the other hand, the median PFI on caelyx/doxil was found to be comparable or to exceed the median PFI of all prior therapies in such patients supporting the hypothesis that progression-free status may be lengthened by such maintenance.

Reinforcing our hypothesis that caelyx/doxil treatment may be necessary in order to maintain some intratumoral doxorubicin concentration within otherwise undetectable nodules, are the relapses observed in four patients on long-term maintenance. In three of these patients, relapses appeared to occur after the treatment interval was lengthened beyond 6 weeks. Objective coupled with CA 125 responses were achieved in these patients by adding carboplatin and this appeared to ‘recapture’ the ability of caelyx/doxil to maintain the response. While one cannot dismiss the notion that the prolonged control of disease is entirely due to reintroduction of the platinum, this is highly unlikely since in all three patients the duration of response from their initial prior carboplatin treatment has already been surpassed. The mechanism of postulated continued efficacy without eradicating the tumor cells in such a maintenance mode remains conjectural, with effects against the tumor vasculature being an attractive possibility.

In summary, our experience indicates that long-term maintenance with caelyx/doxil in patients with ovarian cancer at risk of relapse is safe and likely extends the PFI. The issue of maintenance with caelyx/doxil in the management of relapsed ovarian cancer urgently needs to be addressed in prospective first and second-line trials. Although a similar strategy is applicable to other drugs used in second line, caelyx/doxil has...
several practical advantages as an option for maintenance indicated by our experience: a long dosing interval, near absence of acute or chronic toxic effects except for dermatologic, and no need for any accompanying premedication or special venous access requirements.

acknowledgements

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references


