Docetaxel and oxaliplatin in the second-line treatment of platinum-sensitive recurrent ovarian cancer: a phase II study

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Background: A prospective phase II study was conducted to evaluate the efficacy and toxicity of the combination docetaxel (Taxotere) (DTX) and oxaliplatin (OXA) in ovarian cancer patients recurring after a platinum-free interval (PFI) >12 months.

Patients and methods: DTX, 75 mg/m², was administered by 60 min i.v. infusion, followed by OXA, 100 mg/m², given by a 2 h i.v., on day 1 every 21 days.

Results: From October 2003 to June 2006, 43 ovarian cancer patients were enrolled. Median PFI was 26 months. All patients were available for response evaluation: 17 complete responses and 12 partial responses were registered, for an overall response rate of 67.4%. The median response duration was 10 months. Stable disease was documented in 11 patients (median duration = 5.5 months). The median time to progression and overall survival were 14 and 28 months. A total of 259 courses were administered. Grade 3–4 leukopenia was documented in 32.5% of the patients, while no case of severe anemia and thrombocytopenia was observed. Grade 3–4 neurotoxicity and grade 2 alopecia were observed in 9.3% and 34.9% of cases, respectively.

Conclusion: DTX/OXA combination is an active regimen with a favorable toxicity profile, for treatment of recurrent platinum-sensitive ovarian cancer patients.

Key words: docetaxel, ovarian cancer recurrence, oxaliplatin

introduction

Ovarian cancer is the fifth most frequent cancer in women, and is the leading cause of death among gynecological malignancies [1]. Most patients are diagnosed with already advanced disease, so that despite the surgical efforts aimed at achieving optimal cytoreduction and the use of platinum/paclitaxel (Taxol®; Bristol-Myers Squibb, Princeton, NJ) regimen [2, 3] prognosis is still unfavorable [1–3].

Only a small proportion of recurrent ovarian cancer patients may benefit from surgical treatment of recurrence [4], since in most cases ovarian cancer patients recur with diffuse carcinomatosis or multiple nodule abdominal disease [5], and require medical treatment. The choice of the drug or drug combinations to be used at recurrence is conditioned by the duration of platinum-free interval (PFI); indeed, patients recurring within 6 months from completion of primary chemotherapy are considered platinum resistant and are usually triaged to salvage nonplatinum chemotherapy, while cases with a PFI >6 months are considered platinum sensitive and exhibit rates of response to platinum-based rechallenge, ranging from 27% to 59% according to the duration of PFI [6–8].

Following several phase II studies showing that the addition of paclitaxel to platinum provides a higher response rate and a longer time to progression (TTp) in platinum-sensitive recurrent ovarian cancer compared with historical controls treated with platinum alone [9–13], a pooled analysis of phase III trials (ICON4/AGO-OVAR-2.2) has been recently published, demonstrating the improvement of TTp and overall survival (OS) associated with platinum/paclitaxel rechallenge. However, considerable toxicity in terms of sensory neuropathy (up to 20% of cases) and alopecia (86% of cases), which both play a negative role on patients’ quality of life, has been documented with this regimen [14].

Therefore, efforts are ongoing to define effective platinum-based combinations or schedules with a more favorable toxicity profile. In particular, the use of paclitaxel [13, 15] or paclitaxel/carboplatin [16] on a weekly schedule has been explored, as well as the combination of carboplatin with other cytotoxic
study or expose the patient to extreme risk. Unrelated to malignancy which would limit full compliance with the metastases; uncontrolled severe infection and/or medical problems and borderline ovarian tumors; symptomatic central nervous system and no residual neurotoxicity from previous platinum/paclitaxel regimen.

A phase II trial in platinum-sensitive recurrent ovarian cancer patients with the combination OXA/paclitaxel has been very recently published documenting a high level of activity, but with considerable toxicity [23].

The aim of this open-label phase II study was to investigate the efficacy and toxicity profile of the combination DTX and OXA in platinum-sensitive recurrent ovarian cancer patients on the basis of the proven activity of these drugs in this neoplasia and their acceptable toxicity profile [19–21].

**materials and methods**

**study design**

This is a multicenter phase II study aimed at evaluating the activity of the combination of DTX and OXA in recurrent platinum-sensitive ovarian cancer patients. Since patients recurring between 6 and 12 months from completion of primary chemotherapy experience rates of response to platinum or platinum/paclitaxel rechallenge between 27% and 33%, which are lower compared to cases with a PFI [8], this study was designed with more stringent inclusion criteria for platinum sensitivity, thus including only patients with a PFI >12 months.

The primary end point was the assessment of DTX/OXA efficacy in terms of clinical response and TtP. OS as well as the evaluation of safety and tolerability of the combination were also assessed as secondary end points. The approval of the local ethic committee was obtained before start of the trial.

**eligibility**

Patients with histologically documented epithelial ovarian cancer recurring after a period of >12 months from completion of primary chemotherapy, and previously treated with only one platinum/paclitaxel regimen were enrolled. Only cases with radiological evidence of measurable (>2 cm) lesions were eligible for the study. Further entry criteria were as follows: age 18–75 years, Eastern Cooperative Oncology Group performance status of 2 or less, life expectancy >3 months, absolute neutrophil count (ANC) >1500/µl, platelets count >150 000/µl, bilirubin and creatinine levels <1.5 times the upper limit of normal, normal cardiac and respiratory functions, and no residual neurotoxicity from previous platinum/paclitaxel regimen. Before entry study, all patients were required to provide a written informed consent to the protocol.

Exclusion criteria were as follows: previous or concurrent malignancies at other sites with the exception of basal or squamous cell carcinoma of the skin and cone biopsied carcinoma in situ of the uterine cervix; Brenner’s and borderline ovarian tumors; symptomatic central nervous system metastases; uncontrolled severe infection and/or medical problems unrelated to malignancy which would limit full compliance with the study or expose the patient to extreme risk.

**treatment plan**

Within 14 days from the beginning of the study treatment, patients were submitted to a complete clinical evaluation (including computed tomography scan), laboratory tests, with complete blood cell count, serum chemistry, CA 125 level, and urinalysis.

DTX, 75 mg/m², was administered on day 1 by 60 min i.v. infusion, followed by OXA, 100 mg/m², given by a 2 h i.v.; cycles were repeated every 21 days. All patients received an antiemetic prophylaxis (metoclopramide) before the application of chemotherapy. Complete blood count and platelet count were carried out on a weekly basis; a routine 12-channel biochemistry was carried out on days 1, 8, and 14 of each cycle, unless differently indicated.

Chemotherapy-induced toxicity was graded according to the National Cancer Institute–Common Toxicity Criteria [24]. In the case of hemoglobin <9 g/dl, ANC <1000/µl and/or platelet (PLT) <100 000/µl, treatment was postponed by 1 week. In patients who had delayed treatment for >2 weeks and in case of development of hypersensitivity reactions, treatment was discontinued. In case of ANC <500/µl or PLT <50 000/µl for >5 days, DTX and OXA doses were reduced by 20% in the next cycle. In case of neurotoxicity greater than or equal to grade 2, treatment was postponed by 1 week and DTX/OXA doses were reduced by 20% in the next cycle. Granulocyte colony-stimulating factor (G-CSF) and/or epoetin were administered in the cases of hematological toxicity according to the American Society of Clinical Oncology guidelines [25].

CA 125 levels were tested on day 1 of each cycle, while clinical evaluation (including computed tomography scan) was planned every two cycles. Clinical response was assessed according to the Response Evaluation Criteria in Solid Tumors criteria [26]. Response rate was calculated including 95% confidence intervals. In addition, response was also assessed according to the criteria proposed by Rustin et al. [27].

**statistical analysis**

The sample size was calculated based on the two-stage design by Simon [28]. The design tested the null hypothesis that the true response rate for this population would improve by <50%, i.e. from 45% to the clinically relevant alternative of 70%, using an α error of 0.05 and a β error of 0.2. The sample size was quantified based on the retrospective analysis by Markman et al. [8] showing that the single-agent platinum as second-line treatment of ovarian cancer patients recurring >12 months from completion of primary chemotherapy provided a response rate ~45%. Thus, the first step was planned to include 15 patients; if ≥8 patients responses were recorded, the study would enroll additional 28 patients up to a total number of 43 patients. The regimen would be considered active if ≥26 responses are recorded.

OS was defined as time elapsed between start of DTX/OXA treatment and date of death or the date last seen. TtP was defined as the time elapsed between start of DTX/OXA treatment and documentation of progressive disease or the date last seen. Median and life tables were computed using the product-limit estimate by the Kaplan–Meier method [29].

**results**

**patient characteristics**

From October 2003 to June 2006, a total of 43 ovarian cancer patients recurring >12 months from completion of primary chemotherapy were enrolled into this phase II clinical trial. At initial diagnosis, patient median age was 57 years (range 27–74), and 83.7% were stage III–IV disease. Thirty-eight cases (88.4%) had serous histology and 80.5% tumors were poorly differentiated. Twenty-six patients (60.5%) underwent optimal cytoreduction (maximal diameter of residual tumor ≤1 cm), while three (6.9%) patients had suboptimal (maximal diameter of residual tumor ≥1 cm), and 15 (34.9%) patients
were considered unresectable at primary surgery and underwent neo-adjuvant chemotherapy before attempting secondary cytoreduction.

Patient characteristics at diagnosis of recurrence are detailed in Table 1. Median age was 60 years (range 28–76). Median PFI was 26 months (range 13–91); in particular, 21 patients (48.9%) had a PFI 13–24 months, while 22 patients (51.1%) had a PFI >24 months. CA 125 levels at diagnosis of recurrence ranged from 16 to 5596 IU/ml (median value 179 IU/ml).

Recurrences included nine cases of diffuse carcinomatosis (with target lesions represented by nodules of >1 cm diameter), 12 lymph node recurrences, five pelvic recurrences, localization of disease in the liver (n = 1), spleen (n = 1), and abdomen (n = 2), and 13 cases of multiple intrabdominal lesions.

response to treatment
At the time of analysis, all patients were available for response evaluation (Table 2). In the overall series, 17 complete responses (CRs) (39.5%) and 12 partial responses (PRs) (27.9%) have been registered, with an overall response rate of 67.4%. Moreover, 11 patients (25.6%) experienced stabilization of disease, with a rate of overall clinical benefit (CR, PR, SD) of 93.0%. The percentage of cases achieving CR or PR to treatment was higher (77.3%) in patients with a PFI >24 months compared to cases with a PFI between 13 and 24 months (57.1%), although the difference did not reach the statistical significance (P value = 0.2).

Based on previously published data relative to the unfavorable prognosis of cases recurring as diffuse carcinomatosis compared with single-nodule or multiple-nodule localization of recurrence, we were prompted to investigate whether there could be a different susceptibility to treatment according to type of recurrence; no statistically significant difference in the proportion of responders according to type of recurrent disease was documented (70.0% in cases with diffuse carcinosis versus 65.2% in cases with discrete lesions, P value = 0.7).

Table 1. Patient characteristics at diagnosis of recurrence

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled</td>
<td>43</td>
</tr>
<tr>
<td>Age, years (median, range)</td>
<td>60, 28–76</td>
</tr>
<tr>
<td>Performance status 0/1/2</td>
<td>21/20/2</td>
</tr>
<tr>
<td>Median PFI (range)</td>
<td>26 (13–91)</td>
</tr>
<tr>
<td>CA 125 levels (IU/ml)</td>
<td>179 (16–5596)</td>
</tr>
<tr>
<td>Type of recurrence</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>20 (46.5%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>14 (32.5%)</td>
</tr>
<tr>
<td>Diffuse carcinosis</td>
<td>9 (20.9%)</td>
</tr>
<tr>
<td>Site of recurrence</td>
<td></td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>9 (20.9%)</td>
</tr>
<tr>
<td>Lymphnodes</td>
<td>12 (27.9%)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>5 (11.6%)</td>
</tr>
<tr>
<td>Liver/spleen</td>
<td>2 (4.6%)</td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>2 (4.6%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>13 (30.2%)</td>
</tr>
</tbody>
</table>

PFI, platinum-free interval.

According to Rustin [27] criteria, a 50% CA 125 response occurred in 26 of 35 patients (74.3%) showing elevated CA 125 levels at diagnosis of recurrence.

survival analysis
Follow-up data were available for all patients. As of October 2006, median follow-up duration was 19 months (range 3–46). During the follow-up period, progression and death of disease were observed in 27 and 14 cases, respectively. Median TTP and OS were 14 and 28 months, respectively (Figure 1).

toxicity
A total of 259 courses are evaluable for toxicity, with a median number of six cycles (range 2–11) having been administered per patient (Table 3).

The median cumulative dose of DTX and OXA per patient were 450 mg/m<sup>2</sup> and 600 mg/m<sup>2</sup>, respectively. As far as hematologic toxicity is concerned (Table 4), grade 3, 4 leukopenia affected 13 (30.2%) and one (2.3%) patients, respectively, for a total of 35 cycles (13.5%) and grade 3, 4 neutropenia was documented in 26 patients (60.5%) for

Table 2. Clinical response in the overall series

<table>
<thead>
<tr>
<th>Response</th>
<th>No.</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>17</td>
<td>39.5 (24.9, 54.1)</td>
</tr>
<tr>
<td>Partial</td>
<td>12</td>
<td>27.9 (14.5, 41.3)</td>
</tr>
<tr>
<td>Overall</td>
<td>29</td>
<td>67.4 (53.4, 81.4)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11</td>
<td>25.6 (12.6, 38.6)</td>
</tr>
<tr>
<td>Progression</td>
<td>3</td>
<td>6.9 (–0.7, 14.5)</td>
</tr>
<tr>
<td>Clinical benefit (CR, PR, SD)</td>
<td>40</td>
<td>93.0 (85.4, 100.6)</td>
</tr>
</tbody>
</table>

Table 3. Clinical response to treatment

<table>
<thead>
<tr>
<th>Time to response (months)</th>
<th>No.</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>2.5 (1.2–8)</td>
<td></td>
</tr>
<tr>
<td>Duration of response (months)</td>
<td>10 (1–44)</td>
<td></td>
</tr>
<tr>
<td>Stabilization of disease (months)</td>
<td>5.5 (2.5–10.7)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

Figure 1. Time to progression (TTP) and overall survival (OS) curves in the overall series.
a total of 78 cycles (30.1%). No case of febrile neutropenia was observed. Myelosuppression was usually brief and manageable with dose adjustments or treatment delay. Three patients (6.9%) required administration of G-CSF for a total of 17 cycles (6.6%), because of grade 4 neutropenia persisting for >5 days. No case of moderate/severe anemia was documented. No case of moderate/severe thrombocytopenia occurred.

This schedule is associated with a favorable non-hematologic toxicity profile (Table 5): grade 3 asthenia was registered in only one patient (2.3%), while grade 2 alopecia was documented in 15 cases (34.9%), although no scalp cooling was adopted. Grade 3 diarrhea, nausea, and vomiting occurred in five (11.6%), four (9.3%) and one (2.3%) patient, respectively. Moderate anorexia occurred in two patients (4.6%).

Overall, grade 2, 3 sensory neuropathy was documented in seven (16.3%) and four (9.3%) patients, respectively. No case of severe sensory neurotoxicity or motor neuropathy was observed. All cases experiencing grade 2, 3 sensory neuropathy recovered from neurotoxicity within 13 months from completion of chemotherapy (median 5 months, range 2–13).

Table 3. Study drug administration details

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cycles administered</td>
<td>239</td>
<td></td>
</tr>
<tr>
<td>Cycles with dose reduction</td>
<td>34  (13.1%)</td>
<td></td>
</tr>
<tr>
<td>Delayed cycles</td>
<td>2  (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Median no. of cycles per patient</td>
<td>6  (2–11)</td>
<td></td>
</tr>
<tr>
<td>Median cumulative DTX dose, mg/m² (range)</td>
<td>450 (150–825)</td>
<td></td>
</tr>
<tr>
<td>Median cumulative OXA dose, mg/m² (range)</td>
<td>600 (200–1000)</td>
<td></td>
</tr>
</tbody>
</table>

DTX, docetaxel; OXA, oxaliplatin.

Table 4. Hematological toxicity (n = 43)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1 No.</th>
<th>Grade 2 No.</th>
<th>Grade 3 No.</th>
<th>Grade 4 No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>7 16.3</td>
<td>19 44.2</td>
<td>13 30.2</td>
<td>1 2.3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 4.6</td>
<td>11 25.6</td>
<td>11 25.6</td>
<td>15 34.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 25.6</td>
<td>4 9.3</td>
<td>0 –</td>
<td>0 –</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 11.6</td>
<td>1 2.3</td>
<td>0 –</td>
<td>0 –</td>
</tr>
</tbody>
</table>

Table 5. Non-hematological toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1 No.</th>
<th>Grade 2 No.</th>
<th>Grade 3 No.</th>
<th>Grade 4 No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>6 13.9</td>
<td>8 18.6</td>
<td>1 2.3</td>
<td>0 –</td>
</tr>
<tr>
<td>Hair loss</td>
<td>4 9.3</td>
<td>15 34.9</td>
<td>– – – –</td>
<td>– – – –</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 13.9</td>
<td>1 2.3</td>
<td>5 11.6</td>
<td>0 –</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 23.2</td>
<td>13 30.2</td>
<td>4 9.3</td>
<td>0 –</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 20.9</td>
<td>6 13.9</td>
<td>1 2.3</td>
<td>0 –</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6 13.9</td>
<td>5 11.6</td>
<td>2 4.6</td>
<td>0 –</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>13 30.2</td>
<td>7 16.3</td>
<td>4 9.3</td>
<td>0 –</td>
</tr>
<tr>
<td>Liver</td>
<td>7 16.3</td>
<td>2 4.6</td>
<td>1 2.3</td>
<td>0 –</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>2 4.6</td>
<td>3 6.9</td>
<td>0 –</td>
<td>0 –</td>
</tr>
</tbody>
</table>

Grade 3 hepatotoxicity was documented in one case (2.3%), while cutaneous toxicity (only grade 1, 2) affected five patients (11.6%). A case of pharyngolaryngeal dysphasia related to OXA administration was documented. In 10 patients (23.2%), a 20% dose reduction for a total of 34 cycles (13.1%) was required because of the occurrence of grade 2, 3 neurotoxicity (five patients) and grade 4 neutropenia lasting >5 days (five patients). One-week delay was necessary in two patients (4.6%) for a total of two cycles (0.8%). There were no patients discontinuing treatment because of chemotherapy toxicity.

**discussion**

This is the first study aimed at assessing the efficacy and safety of the combination OXA/DTX in recurrent ovarian cancer patients with a PFI >12 months. We showed that DTX/OXA combination provides an overall response rate of 67.4%, which compares favorably with results of earlier phase II studies, although it has to be acknowledged that comparison of response rates across nonrandomized phase II studies is difficult, especially in light of the heterogeneity and patients’ selection issues. Our data seem even more encouraging considering the rate of disease stabilization (25.6% with a median duration of 5.5 months) and the overall clinical benefit in 93% of cases. These figures well reflect on survival outcome since median TtP and OS were 14 and 28 months, respectively.

Although it can be argued that the selection of cases with a PFI >12 months in the current study could lead to expectedly more favorable results, it has also to be considered that all patients in our series had received previous taxanes compared with 43% and 76% of previous studies [14, 23], and this observation becomes clinically relevant considering that, although this issue has been not specifically addressed, median TtP has been reported to be lower in recurring ovarian cancer patients receiving platinum/taxanes after a previous taxane exposure [14, 23].

One of the major concerns in platinum/taxane-based regimens is represented by non-hematological toxicity; in particular, grade 2–4 sensory neuropathy approached 20% in ICON4/AGO-OVAR-2.2 trial, even though patients with moderate/severe neurotoxicity after first line were excluded from the study. Moreover, an overall grade 2–3 neurotoxicity rate of 69% has been documented by Viens et al. [23], utilizing OXA/paclitaxel treatment. In addition, it has to be considered that the proportion of neurotoxicity would be expected to be even higher considering that only 43% of cases in ICO4/AGO-OVAR-2.2 trial and 76% of cases in Viens’s study [23] had been treated with previous taxanes [14]. Indeed, considering the current widespread use of carboplatin/paclitaxel combination as first-line chemotherapy, and, above all, the significant proportion and duration of residual neurotoxicity after this regimen [30], much attention has to be focused on the choice of drugs to be used for rechallenge of potentially platinum-sensitive disease.

Among regimens utilizing the combination of platinum and taxanes, as second-line treatment of platinum-sensitive recurrent ovarian cancer patients, our combination was shown to exhibit an encouraging neurotoxicity profile, with
grade 2, 3 neuropathy observed in 16% and 9% of cases. Moreover, the percentage of patients recovering from neuropathy and also the median time of neurotoxicity resolution (5.5 months) appear favorable. In addition, grade 2 alopecia has been reported in 34.9% of cases, which represents a very favorable result. In this context, the use of weekly platinum/taxane schedule with apparently equivalent efficacy in terms of response and duration of progression-free survival and reduced neuropathy and alopecia have been explored [16, 18]. Moreover, combinations of platinum with other drugs such as gemcitabine or pegylated liposomal doxorubicin have been recently investigated [17, 31].

The combination gemcitabine/carboplatin has been reported to provide a significant improvement of response rate and progression-free survival, and a tolerable non-hematological toxicity profile in recurrent platinum-sensitive ovarian cancer patients compared with platinum alone [17]. Unfortunately, this regimen was characterized by a very high rate of grade 3, 4 hematological toxicity up to 27%, 72%, and 32% for anemia, neutropenia, and thrombocytopenia, despite the use of hematopoietic growth factors and red blood cell transfusions in ~24% and 27% of cases, respectively.

In this context, encouraging efficacy and safety results from a phase II study exploring carboplatin/pegylated liposomal doxorubicin in recurrent platinum-sensitive ovarian cancer patients have prompted the launch of a multinational randomized phase III Gynecologic Cancer Intergroup trial comparing carboplatin/pegylated liposomal doxorubicin versus carboplatin/paclitaxel in ovarian cancer patients recurring with a PFI >6 months (CAeL.Yx in Platinum Sensitive Ovarian Cancer Patients study).

In conclusion, DTX/OXA combination was shown to be active in recurrent platinum-sensitive ovarian cancer patients, and to provide an acceptable toxicity profile, thus representing an interesting option to be eventually investigated in future trials in this subset of patients, taking also into account that neither DTX nor OXA are currently approved for treatment of ovarian cancer.

The role of DTX/OXA combination in the treatment of platinum resistant ovarian cancer patients has been never investigated: both drugs have shown incomplete cross-resistance with parent compounds [31, 32]; however, clinical data by Fracasso et al. [34], seem to indicate that at least the activity of OXA in this subset of patients is limited.

acknowledgements

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references