**Front-line window therapy with cisplatin in patients with primary disseminated Ewing sarcoma: A study by the Associazione Italiana di Ematologia ed Oncologia Pediatrica and Italian Sarcoma Group**

***Title:***

Front-line window therapy with cisplatinum in patients with primary disseminated Ewing sarcoma: a study of Associazione Italiana di Ematologia ed Oncologia Pediatrica and Italian Sarcoma Group.

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***Abstract***

Patients with Ewing sarcoma metastatic at skeleton and/or viscera at onset (primary disseminated) have a dismal prognosis and new treatments are urgently needed. The aim of the present prospective phase II study was to evaluate the activity of cis-diamino-platinum 120 mg/sqm every 3 weeks for 2 courses as front-line window therapy in a cohort of children and young adults with primary disseminated Ewing sarcoma. Twelve consecutive patients were enrolled in the stage 1 according to a Simon two-stage design, and one objective response according to RECIST Criteria was observed, and therefore the statistical target of response rate > 8% was not achieved. For this reason, the accrual was stopped and CDDP as single-agent was not considered for further evaluation in primary disseminated Ewing sarcoma.

***Introduction***

The prognosis for with Ewing sarcoma metastatic at skeleton and/or viscera at onset (primary disseminated) remains dismal (1-4). Standard chemotherapy for Ewing sarcoma (ES) include different combinations of vincristine, cyclophosphamide, ifosfamide, etoposide, doxorubicin and actinomycin-D (5). Recently, topotecan, irinotecan and temozolomide were included in ongoing front-line clinical trials due to the promising activity of these drugs in phase I-II studies in relapsed/refractory ES (6-10).
Cis-diamino-platinum (CDDP) was studied in a limited number of clinical trials either in first line or at relapse, and results of its use as single agent are limited to one paper (11-21).
In the present prospective study of Italian Sarcoma Group (ISG) and Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP), we evaluated the activity of two courses of CDDP as single agent as a front-line window therapy in a cohort of patients with primary disseminated ES at onset.

***Materials and methods***

The ISG/AIEOP Very-High Risk-2 (VHR-2) study (Eudract 2005-002561-36) enrolled patients with primary disseminated ES at onset. All scientific/ethical committees of the involved institutions approved the protocol, and informed consent was obtained from adult patients or from the legal guardians. ISG/AIEOP VHR2 consisted of CDDP 120 mg/sqm delivered in continuous infusion for 48 hours every 3 weeks for 2 courses as front-line window therapy, followed by the intensive program previously described according to the ISG/SSG IV study (22). The primary aim of the VHR-2 study was the evaluation of the overall response rate after the 2 courses with CDDP according to the Response Evaluation Criteria in Solid Tumours 1.1 (RECIST) (23). Secondary end points included safety profile of the front-line window therapy, and outcome of the whole VHR-2 strategy measured as 2-year event-free survival and 2-year overall survival rates.
Eligibility criteria included histologically proven diagnosis of ES, presence of multiple skeletal metastases and/or visceral metastases at onset, with/without lung metastases. Initial evaluation included CT or MR of the primary tumor, TC99 scan, chest and abdominal CT scan, bilateral bone marrow aspirate and biopsy. Measurable targets according to the RECIST criteria were mandatory (23). After the 2 CDDP courses (week 6), a complete re-evaluation was performed, and the response was evaluated with RECIST criteria. Response rate was defined as the percentage of evaluable patients with complete response (CR) or partial response (PR). The histological diagnosis and the radiological evaluation before and after the front-line therapy were centrally reviewed. Full blood count and serum chemistry were performed before and after each course of therapy, and adverse events were graded according to the NCIC criteria Version 3.0 (24).
A Simon two-stage design was applied to assess the activity of this strategy with front-line CDDP therapy (25). Under the assumptions that objective response rate (ORR) $\leq$ 8% was considered unacceptable versus $\geq$30% ORR as acceptable and 10% types I and II error rates,12 patients were to be treated in the first stage. At least 2 objective responses were required to enroll additional 13 patients in the second stage. By this design, the front-line window therapy would be considered ineffective if fewer than 4 responses were obtained for a cohort of 25 patients.
Event-free survival (EFS) was defined as the period from the start of chemotherapy to the most recent follow-up or tumor progression/recurrence or death from treatment-related complications or secondary malignancy. Overall survival (OS) was calculated from the start of chemotherapy to the most recent follow-up or death. Survival curves were calculated according to the Kaplan and Meier method and compared using the log-rank test.

***Results***

In the study-period 2006-2008, 12 consecutive patients with primary disseminated ES at onset were enrolled in the first stage of the study. All patients received the 2 scheduled courses with CDDP and were eligible for response evaluation. Demographics are depicted in Table 1. Responses are described in Table 2. The response rate was 8%, since 1/12 obtained a PR. The characteristics of this patient have been previously described (26). Stable disease (SD) was observed in 9 (75%) and 2 patients had progressive disease (17%) after the second course CDDP.

The major toxicity of the two courses CDDP was hematological. Grade 3-4 neutropenia and grade 3-4 thrombocytopenia occurred after 37% and after 49% of courses, respectively. Platelet transfusions were given after 4 courses (2 patients-1 unit; 1 patient-2 units), while packed red cell transfusions were given after 5 courses in 4 patients (median: 2 units, range 1-4). Additional acute toxicities recorded were grade 3 nausea and grade 3 vomiting during 2 courses in 2 patients, and transient grade 1 hypokalemia during 3 courses (2 patients).

Two-year EFS probability was 0.15 ± 0.14 and 2-year OS probability was 0.22 ± 0.12. The median time to disease progression/relapse with the ISG/AIEOP VHR-2 treatment plan was 11 months (range 1–35). Only one patient (pt #7) is long-term survivor, relapse-free 8 years after the end of the treatment (26).

***Discussion***

CDDP has synergistic effects with other agents in pre-clinical models in ES (27). After the first promising results obtained three decades ago as a single agent, CDDP was included in different phase II trials in relapsed ES (11-18). The responses rates ranged from 18% (cisplatinum+etoposide) to 29-51% (CDDP + ifosfamide + etoposide). (11-18). In this setting, the activity of every single agent was jeopardized by the concomitant use of different drugs and, therefore, it was not possible to determine the contribution, if any, of CDDP to the response rate. However, despite an interesting response-rate, the survival probabilities with the combinations that included CDDP were not superior to other combinations not including CDDP, and were even comparable to the results obtained with oral etoposide alone (6-10,28,29).

Other platinum compounds were tested in resistant/ relapsed ES. Carboplatin is an analogue of cisplatin with less non-hematologic toxicity than the parent compound (30). Although single agent data in carboplatin was limited, combinations of carboplatin + etoposide and ifosfamide or cyclophosphamide have shown promise in relapsed paediatric sarcomas including also ES. These combinations resulted in a substantial response rate in previously treated patients, but with significant toxicity and short-time responses (16, 31-34). Oxaliplatin, a third generation platinum agent containing a DACH (1, 2 diaminocyclohexane) carrier ligand, was developed to provide a less toxic and more effective platinum compound (35). Despite a favourable toxicity prophile, oxaliplatin administered as a single agent had limited activity in childhood relapsed or refractory solid tumors, including ES, where 1 stable disease and 9 progressions were observed in 10 evaluable patients (36).

The peculiarity of the present prospective study is the use of CDDP as single agent in a front-line setting deemed as the most appropriate to ascertain the real activity of this drug in this sarcoma. One objective response (8%) in the stage 1 cohort with 12 consecutive patients enrolled was observed, and therefore the statistical target of RR > 8% was not achieved. For this reason, the accrual was stopped and CDDP as single-agent was not considered appealing for further evaluation. The 2-year EFS and 2-year OS probabilities obtained with ISG/AIEOP VHR-2 confirmed the lack of impact of the use of 2 courses CDDP on the outcome. These results are in fact comparable with those obtained with the previous AIEOP/ISG VHR1 study and with those reported in literature (1-6,37,38). Despite this negative result, one patient treated with CDDP obtained a partial response that traced the path for the achievement of a complete remission with the following treatment according to the Study Protocol (26).

In conclusion, the results obtained with the present study in a front-line setting confirm a limited activity of CDDP in the treatment of Ewing's sarcoma.

**Formattato:** Inglese (Stati Uniti)

***Table 1. Patient characteristics at diagnosis***

| Pt # | Age | Site of the primary tumor | Bone metastases | Lung metastases | Bone marrow infiltration | Other metastatic sites |
|---|---|---|---|---|---|---|
| 1 | 7 | Vertebra | Yes | Yes | No | No |
| 2 | 14 | pelvis | Yes | Yes | No | No |
| 3 | 18 | pelvis | Yes | No | No | No |
| 4 | 21 | vertebra | No | Yes | No | Yes (liver) |
| 5 | 36 | vertebra | Yes | No | No | No |
| 6 | 7 | Tibia | Yes | Yes | Yes | No |
| 7 | 10 | humerus | Yes | No | No | Yes (distant lymph nodes) |
| 8 | 10 | pelvis | Yes | No | No | Yes (distant lymph nodes) |
| 9 | 13 | vertebra | Yes | No | No | No |
| 10 | 12 | scapula | Yes | No | Yes | No |
| 11 | 14 | paravertebral , C7-D1 | Yes | No | No | No |
| 12 | 19 | femur | Yes | Yes | No | No |

***Table 2. Response to the front-line therapy with CDDP according to RECIST Criteria***

| Pt # | Site of the primary tumor | Bone metastases | Lung metastases | Other metastatic sites | Non target lesions | New lesions | Overall response |
|---|---|---|---|---|---|---|---|
| 1 | SD | NE | PD | | PD | Yes | PD |
| 2 | SD | SD | SD | | SD | No | SD |
| 3 | SD | SD | | | | No | SD |
| 4 | SD | | PR | PD | | Yes | PD |
| 5 | SD | SD | | | | No | SD |
| 6 | SD | SD | | | SD | NE | SD |
| 7 | PR | PR | | PR | | No | PR |
| 8 | PR | PD | | PD | SD | No | PD |
| 9 | SD | SD | | | | No | SD |
| 10 | SD | SD | | | CR | No | SD |
| 11 | SD | SD | | | | No | SD |
| 12 | PD | PD | PD | | | Yes | PD |

CR, complete remission; PR, partial remission; SD , stable disease; PD, progressive disease; NE, not evaluated

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