Docetaxel, Ifosfamide and Cisplatin (DIP) in Squamous Cell Carcinoma of the Head and Neck

POL M. SPECENIER, JAN VAN DEN BRANDE, DIRK SCHRIJVERS, MANON T. HUIZING, SEVILAY ALTINTAS, JOKE DYCK, DANIELLE VAN DEN WEYNGAERT, CARL VAN LAER and JAN B. VERMORKEN

Departments of Medical Oncology, Radiotherapy and Otolaryngology, Antwerp University Hospital, Edegem; Department of Medical Oncology, ZNA Middelheim, Antwerp, Belgium

Abstract. Background: Docetaxel, ifosfamide and cisplatin have all shown activity in squamous cell carcinoma of the head and neck (SCCHN). The optimal combination of the three drugs is, however, unknown. Considering the favorable results of taxane-containing triplets as induction chemotherapy in locally advanced (LA) SCCHN, DIP (docetaxel, ifosfamide, cisplatin) was studied in this setting as part of a phase I dose- and sequence-exploring study. Patients and Methods: D (60 or 75 mg/m²) was given by 60-min infusion on day 1, I (1000 mg/m²/day), with mesna until 12 hours after I, by 24-h infusion days 1-5, and P (50 or 75 mg/m²) by 24-h infusion on days 1 or 5. The cycles were repeated every 21 days. Toxicities according to the National Cancer Institute Common Toxicity Criteria version 2 (NCI-CTC2) were evaluated weekly and response was evaluated every 2 cycles according to the World Health Organization (WHO) criteria. Thereafter, radiotherapy (RT, cumulative dose 70 Gy) or chemoradiation (CRT), both with conventional fractionation, were planned. Results: Twenty-two patients (18 male, 4 female; age 41-66 years, performance status 0-1, 2 T4N0, 3 T3N2, 11 T4N2, 3 T unknown N3, 1 T1N3 and 2 T4N3) received a median of 4 DIP cycles (range 1-5). Grade 4 neutropenia occurred in 18 patients, grade 3 and 4 thrombocytopenia in 5 and 1 patients, respectively, and grade 3 anemia in 5 patients. Gastrointestinal and mucosal toxicities were generally mild/moderate. Vascular complications (probably not DIP-related) precluded local treatment in two patients. Moreover, one patient died on day 13 of the first DIP (neutropenic sepsis and myocardial infarction). The remaining patients received RT (n=2) or CRT (n=17; 16 of these with gemcitabine). The response to 2 × DIP was 95% (1 complete response, 19 partial responses, 1 stable disease); the complete response rate increased to 42% after 4 × DIP. No dose or sequence effect was evident. The minimum follow-up of the surviving patients was 51 months, with median relapse-free survival of 13.8 months and median overall survival of 18.8 months. Only four patients relapsed at distant sites. Conclusion: DIP is highly active in previously untreated LA SCCHN, however, toxicity of DIP in this population is substantial.

For over two decades, cisplatin has been the backbone of chemotherapeutic regimens which are used for the treatment of patients with squamous cell carcinoma of the head and neck (SCCHN) (1, 2). This is true for the treatment of both patients with recurrent and/or metastatic disease and patients with locoregionally advanced (LA) disease. Ifosfamide and docetaxel used as single agents have also shown promising activity in patients with head and neck cancer (3-13). Docetaxel, ifosfamide and cisplatin have different mechanisms of action and different safety profiles (14-16). The optimal sequence and dose of these agents in combination have never been determined, but were studied by us in a dose- and sequence-exploring phase I study (17). In that study a substantial number of patients with locoregionally advanced head and neck cancer were included. The efficacy and toxicity outcomes of these patients is the subject of the present report.

Patients and Methods

Study design. A subset of patients with LA-SCCHN who were included in a non-randomized single-center dose- and sequence-exploring phase I study which tested the combination of docetaxel, ifosfamide and cisplatin (DIP) in patients with solid tumors are herein analyzed. The phase I study was conducted between May 2000 and October 2004 (17).

Eligibility criteria. The patients were ≥18 years of age, with a performance status of ≤2 according to World Health Organization (WHO) criteria (18) and a life expectancy of at least 12 weeks. Adequate bone marrow, renal and liver functions were required.
Patients with known central nervous system involvement, congestive heart failure, angina pectoris, uncontrolled hypertension and arrhythmia requiring medication, hematological malignancies, history of significant neurological or psychiatric disorders, an active infection, systemic peripheral neuropathy >2 according to National Cancer Institute Common Toxicity Criteria version 2 (NCI-CTC2) (19) and those with prior radiotherapy to the skeleton on >30% of the bone marrow were excluded.

In accordance with the Declaration of Helsinki, International Conference on Harmonisation (ICH) / WHO Good Clinical Practice (GCP) standards, and applicable local laws, all patients provided signed informed consent. The Ethics Committee of the Antwerp University Hospital approved the protocol.

Study objectives. The objective of this report was to summarize the clinical outcome in terms of efficacy and toxicity of the subset of the 22 patients with LA-SCCHN who participated in the earlier mentioned phase I study which had as the primary objective to determine the maximum tolerated dose (MTD) of docetaxel and cisplatin in combination with a fixed dose of ifosfamide.

Treatment. The 22 LA-SCCHN patients included in the phase I study received docetaxel at a dose of 60 mg/m² or 75 mg/m² over 60 minutes on day 1 followed by a bolus of mesna 500 mg/m² and by ifosfamide 1,000 mg/m²/day along with mesna 1,000 mg/m²/day as a 24-h infusion on days 1 to 5 and cisplatin 50 mg/m² or 75 mg/m² over 24 hours on day 5 (schedule A) or 1 (schedule B). Mesna was continued until 12 hours after the end of ifosfamide. Additional mesna was administered either intravenously or orally in cases of hematuria. All the patients received methylprednisolone 32 mg orally, 12 and 3 hours before the docetaxel administration and twice daily thereafter for two days (total number of 5 administrations). An additional dose of methylprednisolone 125 mg was given intravenously on day 1 in order to prevent acute vomiting. Ondansetron 8 mg was administered intravenously on days 1 to 5. Twelve patients received oral ciprofloxacin prophylactically on days 5 to 15 of each cycle. The cycles were repeated every 21 days. Granulocyte colony simulating factors were not allowed. Erythropoietin or darbapoietin was administered at the physician’s discretion. In cases of ifosfamide-induced encephalopathy, the patients were to be treated with methylene blue 50 mg intravenously every 4 hours until 72 hours after the end of the ifosfamide infusion and methylene blue was to be administered prophylactically during the subsequent cycles at a dose of 50 mg, 4 times a day, starting from 4 hours before the start until 72 hours after the end of the ifosfamide infusion (20).

Efficacy and safety evaluation. The patients were evaluated for response according to the WHO criteria (18) and the toxicities were evaluated according to the NCI-CTC2 (19).

Statistics. The data were summarized using number of patients and percentages. Time to locoregional relapse, time to distant metastasis, relapse-free survival and overall survival were calculated using the Kaplan-Meier method (Statistical Package for the Social Sciences (SPSS) version 15; SPSS Inc., Chicago, IL, USA).

Results

Patient population. The patients with locoregionally advanced SCCHN represented the largest subset of patients included in the phase I study (22 patients out of a total of 85). Two of these 22 patients had received prior chemotherapy±radiotherapy for esophageal cancer and non Hodgkin lymphoma, respectively. The patient characteristics are summarized in Tables I and II.

Treatment and toxicity. Details of the received dose and schedule are summarized in Table III. The great majority of patients received DIP with 75 mg/m² docetaxel combined with 50 mg/m² cisplatin (n=8), or 60 mg/m² docetaxel with 75 mg/m² cisplatin (n=12). The median number of DIP cycles was 4 (range 1-5). The subsequent locoregional treatment after DIP was concurrent chemoradiation (n=17; 16 in combination with gemcitabine at a dose of 100 mg/m² weekly and 1 in combination with cisplatin at a dose of 100 mg/m² day 1, 22 and 43 during radiotherapy) or radiotherapy alone (n=2). Three patients did not receive any form of local treatment due to early toxic death (n=1) or early complications precluding adequate locoregional therapy (n=2) (see below). The toxicities that were observed with the DIP regimens are shown in Table IV. Gastrointestinal toxicity was...
mild and not in excess of grade 2 except in one patient (anorexia grade 4). No mucositis was observed during DIP chemotherapy except in two patients (grade 1).

The early complications that precluded further locoregional treatment in two patients included vascular problems i.e. multiple cerebral infarctions in one patient, compromising his general condition and mental status, and lower limb ischemia in the second patient. Hematological toxicity was substantial, with grade 4 neutropenia occurring in 18 patients (82%), grade 3 thrombocytopenia in 5 patients (23%), grade 4 thrombocytopenia in 1 patient (5%) and grade 3 anemia in 5 patients (23%). Febrile neutropenia occurred in 18 patients (36%), 4 of whom had received prophylactic ciprofloxacin. One patient died during the DIP treatment (5%); this patient died on day 13 of cycle 1 due to neutropenic sepsis and myocardial infarction. Out of the 19 patients who continued with locoregional therapy after induction with DIP one died after 18 Gy of radiotherapy and 2 × weekly gemcitabine (100 mg/m²) due to septic shock.

Response and outcome. The number of DIP cycles was left to the physician’s discretion and was based on the observed response and toxicity. All the patients received at least 2 cycles, except the patient that died during the first DIP cycle. Twenty-one patients were evaluable for response after 2 cycles of DIP. At that time 95% of the evaluable patients responded (5% complete and 90% partial responses). Twelve patients were evaluable for response after 4 cycles of DIP; at that time there were 42% complete and 50% partial responses. One patient with stable disease after four cycles received a fifth cycle of DIP, before receiving definitive irradiation. Elective radical neck dissection after completion of the chemoradiation was performed in 6 patients with initial N2 or N3 disease. Five out of the six resection specimens were free of disease. The minimum follow-up of the surviving patients was 51 months (median 53 months). The time to local failure and time to distant metastasis are shown in Figure 1. The relapse-free and overall survival are shown in Figure 2. The median relapse-free survival of all the patients was 13.8 months and the median overall survival was 18.8 months. Eight patients relapsed locally, four at distant sites.

Discussion

The phase I study, from which the present subset was taken, concluded that when use was made of prophylactic antibiotics, the MTD was reached at 75 mg/m² of docetaxel in combination with 5 days of ifosfamide at 1,000 mg/m²/day and 75 mg/m² of cisplatin (17). All the patients in the subset described in this report received doses of DIP below this MTD.

The response rate was high, with 95% of the evaluable patients responding after two cycles of DIP. Hematological toxicity was substantial, with grade 4 neutropenia occurring in 91% of the patients. In contrast, gastrointestinal toxicity was mild and not in excess of grade 2 except in one patient (anorexia grade 4). No mucositis was observed during DIP chemotherapy except in two patients (grade 1).

Prophylactic use of antibiotics seems advisable with this regimen and the incidence of febrile neutropenia (36%) exceeded the commonly recommended 20% threshold for prophylactic use of granulocyte colony stimulating factors (21-23). Table V summarizes the literature on ifosfamide-based chemotherapy regimens in patients with locoregionally advanced SCCHN. Response rates were high in most of the studies, although hematological toxicity was a major drawback in the majority of the studies.

Sanchez Parra et al. (26) added ifosfamide to the classical cisplatin and 5-fluorouracil. Nineteen patients with stage III or stage IV nonmetastatic SCCHN received 100 mg/m² of cisplatin on day 1, 5-fluorouracil 1,000 mg/m²/day as a 24-h infusion on day 1 through 5 and ifosfamide 1,000 mg/m²/day
Table V. Ifosfamide-based combination chemotherapy regimens in locoregionally advanced SCCHN.

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>N</th>
<th>Ifosfamide dose</th>
<th>Other agent(s)</th>
<th>Interval</th>
<th>Neutropenia</th>
<th>Toxic deaths</th>
<th>RR</th>
<th>CR</th>
<th>DCR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantovani et al.</td>
<td>28</td>
<td>1.5 or 2.2 g/m²/d d1-5</td>
<td>Cisplatin 20 mg/m²/d d1-5</td>
<td>28</td>
<td>13%/13%</td>
<td>11%</td>
<td>50%</td>
<td>0</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Pai et al.</td>
<td>207</td>
<td>1.5 g/m²/d d1-5</td>
<td>Cisplatin 15 mg/m²/d d1-5</td>
<td>28</td>
<td>0% 0%</td>
<td>0% 67%</td>
<td>16%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pai et al.</td>
<td>312</td>
<td>2.2 g/m²/d d1-5</td>
<td>Cisplatin 15 mg/m²/d d1-5</td>
<td>28</td>
<td>0% 0%</td>
<td>0% 80%</td>
<td>24%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanchez et al.</td>
<td>19</td>
<td>0.8-1 g/m²/d d2-4</td>
<td>5-FU 1,000 mg/m²/d d1-5</td>
<td>21</td>
<td>42%/21%</td>
<td>16%</td>
<td>50%</td>
<td>17%</td>
<td>83%</td>
<td>10</td>
</tr>
<tr>
<td>Recchia et al.</td>
<td>24</td>
<td>1.2 g/m²/d d1-4</td>
<td>Docetaxel 40-70 mg/m²/d</td>
<td>28</td>
<td>20%/34%</td>
<td>20%</td>
<td>0% 83%</td>
<td>25%</td>
<td>96%</td>
<td>22</td>
</tr>
<tr>
<td>Shin et al.</td>
<td>54</td>
<td>1 g/m²/d d1-3</td>
<td>Paclitaxel 175 mg/m²/d</td>
<td>21-28</td>
<td>9% 2%</td>
<td>81%</td>
<td>31%</td>
<td>87%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Hancock et al.</td>
<td>18</td>
<td>1 g/m²/d d1-3</td>
<td>Paclitaxel 175 mg/m²/d</td>
<td>21</td>
<td>94%</td>
<td>44%</td>
<td>94%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This series</td>
<td>22</td>
<td>1 g/m²/d d1-5</td>
<td>Docetaxel 60 or 75 mg/m²/d</td>
<td>21</td>
<td>14%/82%</td>
<td>36%</td>
<td>5%</td>
<td>95%</td>
<td>23%</td>
<td>100% 18.8</td>
</tr>
</tbody>
</table>

N: Number of patients, FN: febrile neutropenia, RR: overall response rate, CR: complete response rate, DCR: disease control rate, OS: overall survival, ref: reference; a: no prophylactic myeloid growth factors were used, b: hematologic toxicity only occurred in high dose arm, c: also 16% grade 5; § 2-year survival rate, §§: 5% after 2 cycles, 42% after 4 cycles, AUC: area under the concentration-time curve, gr: grade, 5-FU: 5-fluorouracil.

Figure 1. Time to local failure and time to distant metastasis.

Figure 2. Relapse-free and overall survival.
as a 1-hour infusion on day 2, 3 and 4. Mesna 200 mg/m² was given as a bolus prior to and 4 and 8 hours after each ifosfamide administration. The cycles were repeated every 3 weeks for a maximum of three cycles. The overall response rate was 50% with 16.6% complete responses. The study was closed early because of the severe hematological toxicity.

Particularly high response rates were reported when a combination of ifosfamide, a taxane and a platinum compound was used in patients with locoregionally advanced squamous cell carcinoma (27-29). Recchia et al. (27) performed a dose finding study of docetaxel in combination with ifosfamide 1,200 mg/m²/d and cisplatin 20 mg/m²/d, both administered on days 1-4. Docetaxel was administered on day 1 at doses escalating from 40 mg/m² up to the dose limiting toxicity which occurred at 70 mg/m². The cycles were repeated every four weeks. Twenty-four patients received a median of four cycles (range 2-6). Febrile neutropenia occurred in 20% of the patients. The overall response rate after induction chemotherapy was 83% with a complete response rate of 25%.

Shin et al. (28) treated 54 patients with the TIC regimen which consisted of paclitaxel 175 mg/m² by 3-h infusion on day 1, ifosfamide 1000 mg/m² as a 2-h infusion on days 1-3 with i.v. mesna (200 mg/m² before and 400 mg/m² after ifosfamide) and carboplatin using the Calvert formula for an area under the plasma concentration-versus-time curve of 6 mg/ml min on day 1, repeated every 3 weeks. As in the present study and in the study by Recchia et al., prophylactic hematopoietic growth factors and antibiotics were not given. Five patients (9%) developed neutropenic fever. The overall response rate after four cycles was 81%, with 31% complete responses.

Hancock et al. (29) reported on a selected subset of 18 patients with base of tongue cancer treated with up to 3 cycles of paclitaxel 175 mg/m² and cisplatin 60 mg/m², both administered on day 1 followed by ifosfamide 1,000 mg/m² on days 1-3. The overall and complete response rates were 95% and 44%, respectively.

Since the completion of the present study several large randomized studies have been published (30-34), indicating that a taxane, particularly docetaxel (31-34), added to cisplatin and 5-fluorouracil (TPF) yields superior response rates and an improved survival with less toxicity (32) and a better quality of life (34) than the classical cisplatin-5-fluorouracil (PF) regimen, when used as induction chemotherapy in patients with locoregionally advanced head and neck cancer. Recently reported preliminary data on the sequential approach (induction chemotherapy followed by chemoradiation) were promising and the results of the randomized trials, comparing induction chemotherapy followed by concurrent chemoradiation with the current standard concurrent chemoradiation alone, are eagerly awaited (35, 36). However, pending the publication of the final results of these trials, induction chemotherapy should still not be considered standard treatment, which still remains cisplatin-based chemoradiation.

Now that novel targeted agents are rapidly becoming available, DIP will probably never be compared to TPF, which has replaced PF as the standard induction regimen in those cases where induction chemotherapy is considered appropriate. Indeed, priority will most likely be given to the integration of these targeted therapies into the current treatment strategies.

In conclusion, the combination of docetaxel, ifosfamide and cisplatin is very active in locoregionally advanced squamous cell head and neck cancer, but the toxicity (mainly hematological) is substantial.

References


