Alternating gemcitabine and cisplatin with gemcitabine and radiation in stage IV squamous cell carcinoma of the head and neck

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Received 14 October 2003; revised 11 December 2003; accepted 22 December 2003

Background: In order to improve our cisplatin–5-fluorouracil (5-FU)-based alternating chemo-radiotherapy regimen, in 1996 we started an investigational program to explore a modified alternating regimen including gemcitabine given both with radiosensitizing and cytotoxic intent.

Materials and methods: Based on our previous feasibility trial, we conducted a second study testing the feasibility and activity of the following schedule: gemcitabine 800 mg/m2 on day 1 and cisplatin 20 mg/m2 on days 2–5 (weeks 1, 4, 7 and 10) alternated with three courses of radiotherapy (RT) (weeks 2–3, 5–6 and 8–9) with conventional fractionation up to 60 Gy. Gemcitabine 300 mg/m2 was also administered on the Monday of each week of RT.

Results: Forty-seven patients with stage IV (41 patients) unresectable squamous cell carcinoma of the head and neck (SCC-HN) or who had relapsed after surgery (6 patients) were enrolled. None had previously received chemotherapy or radiotherapy. Eight patients (18%) did not complete the treatment. Main grade 3–4 toxicities were as follows: neutropenia (44%); neutropenia with fever (12%); thrombocytopenia (37%); anemia (30% grade 3). One patient died in therapy due to sepsis. Most patients needed hospitalization and tube-feeding or parenteral nutrition. However, 44% of patients had a weight loss >10%. Thirty-four patients had a complete response (72%). Three partial responders were rendered disease-free by surgery (final complete response rate, 79%). At a median follow-up of 38 months actuarial 3-year overall survival, progression-free survival and loco-regional control are 43%, 39% and 64%, respectively. Data of locoregional control favorably compare with those from our database of patients treated with alternating cisplatin–fluorouracil and radiation within controlled clinical trials (64% versus 40%).

Conclusions: The inclusion of gemcitabine into an alternating regimen seems to improve the results achievable with the original alternating program in stage IV patients. However, due to the high acute toxicity correlated, this intensive regimen should be managed by institutions well trained in multidisciplinary treatments.

Key words: chemo-radiotherapy, gemcitabine, head and neck, squamous cell carcinoma, stage IV

Introduction

After three decades of investigation, concomitant chemoradiation can definitely be considered the standard treatment for advanced squamous cell carcinoma of the head and neck (SCC-HN) and a reasonable alternative to front-line radical surgery in operable laryngeal and hypopharyngeal tumors [1].

At present, using the concomitant administration of chemotherapy and radiotherapy, it is reasonable to expect a crude improvement in overall survival (OS) approaching 10% [2], most of this benefit being due to better loco-regional control. However, many questions are still unanswered. In terms of chemotherapy, we still do not know how many drugs and which ones should be used; in addition, we do not know whether a radiosensitizing strategy with low doses of drugs or full-dose chemotherapy is preferable. In terms of radiation, we know that concomitant boost and hyper-fractionation are probably better than standard fractionation, at least in local control [3], but we do not actually know if such an altered fractionation radiotherapy gives a clear clinical benefit besides an increase of local toxicity, even when administered concomitantly with chemotherapy. Finally, we do not know if the addition of induction chemotherapy to a concomitant chemoradiation approach may improve the outcome mainly by reducing the risk of distant metastases. In other words, it has not been demonstrated that more intensive and toxic combined regimens

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achieve better long-term results, since no data from randomized trials comparing different combined approaches are available so far. However, preliminary data from some phase II trials exploring intensive chemoradiation regimens are encouraging [4–6].

At our institution, the standard therapeutic approach to advanced head and neck cancer is alternating cisplatin–5-fluorouracil (5-FU) and radiation [7–9]. In 1996, in an attempt to ameliorate results achieved with this regimen, we started to explore a modified alternating regimen in which 5-FU was replaced with gemcitabine.

Gemcitabine can be considered to be a novel drug in SCC-HN since few experiences are available in this disease both in vitro [10] and in clinical trials [11]. In preclinical studies, this drug has also shown synergistic activity with cisplatin in some human solid tumors cells [12], and in SCC-HN the combination of cisplatin and gemcitabine showed interesting antitumoral activity in one clinical trial [13]. Moreover, gemcitabine, also at non-cytotoxic concentrations, has a proven in vitro [14] and clinical [15] radiosensitization activity in SCC-HN.

Here, we report the results of a phase II trial where gemcitabine was given both with radiosensitizing and cytotoxic intent together with cisplatin and radiation in a modified alternating regimen. The dose of gemcitabine chosen was based on the results of our previous feasibility trial [16] in which the median dose per week actually delivered in an alternating chemo-radiotherapy program was 500 mg/m².

**Materials and methods**

**Selection of patients**

Patients were eligible for the study if they met the following criteria: histologically-proven SCC-HN; stage IV (UICC 1997) previously untreated disease, or who had relapsed after surgery; unresectable lesion; no previous radiotherapy and/or chemotherapy; <76 years of age; performance status <2 [Eastern Cooperative Oncology Group (ECOG) scale] [17]; no major abnormalities of liver, heart, lung and bone marrow function; no distant metastases or other malignancies; life expectancy of ≥3 months; informed consent. Generally tumors were defined as unresectable when resection was considered not technically feasible or radicality was estimated as improbable despite a significant loss of organ and/or organ function.

Pretreatment evaluation included physical and ENT examination, complete blood counts and blood chemistry profiles, and a chest X-ray. Computerized tomography and/or sonograms were performed when indicated.

**Treatment**

The treatment plan is summarized in Figure 1.

Radiotherapy consisted of 60 Gy delivered as a daily single dose of 2 Gy, five times a week. Radiotherapy was planned to be delivered during weeks 2, 3, 5, 6, 8 and 9. Patients were treated with 6 MV photons with shielding blocks. The usual shrinking field technique with lateral parallel opposed photon fields was used to treat the primary site and upper-mid-neck nodes [18]. Fifty Gy were prescribed to electively treat neck regions. The lower neck-supraclavicular regions were treated with an oppositional antero-posterior field. Areas of macroscopic disease were boosted for an additional 10 Gy at 2 Gy per fraction. The dose to the spinal cord was to be limited to 50 Gy.

The chemotherapy regimen consisted of gemcitabine 800 mg/m², day 1 and cisplatin 20 mg/m²/day, days 2–5 of weeks 1, 4, 7 and 10. Gemcitabine 300 mg/m² was administered on day 1 of weeks 2, 3, 5, 6, 8 and 9. Cisplatin was given during a 2-h period of forced hydration and gemcitabine as a 45-min infusion. Antiemetic therapy consisted of dexametason 8 mg intravenously (i.v.) and granisetron 3 mg i.v., before each cisplatin administration and dexametason 8 mg or metoclopramide 20 mg i.v. when gemcitabine was administered alone.

A complete blood cell count was performed on day 1 of each week of treatment. The measurement of serum electrolytes and creatinine was performed...
before each cisplatin-based chemotherapy course. No prophylactic administration of granulocyte colony-stimulating factor was planned. Epoetin α, 10 000 IU subcutaneously every other day, was planned starting at an hemoglobin level <10.0 g/dl.

Chemotherapy dose reductions were planned. In the case of a leukocyte count between 2900 and 2000/ml and/or neutrophil count between 1500 and 1000/ml and/or platelet count between 80 000 and 50 000/ml at the time of cisplatin-based chemotherapy, a 25% dose reduction of both cisplatin and gemcitabine was made. In the case of a leukocyte count <2000/ml and/or neutrophil count <1000/ml and/or platelet count <50 000/ml, the cisplatin-based chemotherapy was delayed for 1 week and the patient received gemcitabine at radiosensitizing dose and continued radiation.

The radiosensitizing dose of gemcitabine was reduced by 50% in the case of leukocyte count between 2000 and 1000/ml and/or neutrophil count between 1000 and 500/ml and/or platelet count between 50 000 and 25 000/ml and it was omitted in the case of leukocyte count <1000/ml and/or neutrophil count <500/ml and/or platelet count <25 000/ml.

**Evaluation of response and toxicity**

The method for staging was repeated to evaluate response to therapy. Response was preliminarily assessed 4 weeks after the end of treatment and definitely assessed after 12 weeks, according to World Health Organization (WHO) criteria [17]. Toxicities were evaluated according to the WHO scale [17] and recorded as the worst grade experienced by patients during the treatment.

**Role of surgery**

Surgery indications were not standardized. Generally a neck dissection was the rule only in patients with clinical and/or radiological evidence of persistent disease in the neck only. Neck dissection was not recommended for patients in complete response (CR) whose disease at diagnosis was staged as N2–3.

**Statistics**

The primary end point of this phase II single institution trial was CR rate assessment. Secondary end points were OS, progression-free survival (PFS) and locoregional control. The expected CR rate with alternating cisplatin–5-fluorouracil and radiation was 45% [7, 9]. Since a significant increase in severe acute mucositis is expected with the inclusion of gemcitabine, this experimental program will be considered suitable for further investigations if the level of CRs is ≥75%. For an α error of 0.05 and a β error of 0.10, at least 26 complete responders are needed among the 41 patients enrolled [19].

Actuarial survival, loco-regional control and PFS are calculated according to the Kaplan–Meier method [20]. All patients were considered in these analyses. PFS was computed from the time of treatment beginning until the time of disease progression at any site, including the occurrence of distant metastases or second primary tumors. Patients dying without disease progression were considered to have had progressive disease at the time of death.

Loco-regional control was computed from the time of treatment beginning until the time of locoregional relapse. Patients developing metastatic disease or second tumors without locoregional relapse were censored at the time of death or last observation. Patients who did not reach the CR, including those who did not complete the treatment program for any reason, were considered locoregionally progressed at the end of treatment. OS was computed from the time of treatment beginning until the time of death or last observation.

**Results**

From March 1998 to August 2001, 47 consecutive patients entered the study. The main patient characteristics are reported in Table 1.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
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<tr>
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<table>
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<tr>
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**Table 2. Tumor (T) and node (N) staging**

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<th></th>
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<th>T2</th>
<th>T3</th>
<th>T4</th>
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<tbody>
<tr>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11</td>
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<tr>
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<td>2</td>
<td>5</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
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<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>36</td>
<td>–</td>
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</table>

Table 1. Tumor and lymph node distribution is presented in Table 2. Forty patients had stage IV unresectable and previously untreated squamous cell carcinoma of the head and neck; seven patients were loco-regionally relapsed after surgery and not eligible for a further resection with radical intent. The primary tumor was staged as T4 in 77% of patients.

Eight patients (17%) did not complete the planned program. One patient died of sepsis during severe neutropenia, two patients died of myocardial infarction and one of acute hepatitis. Four patients discontinued treatment because of peritonitis, arterial thrombosis, cerebral infarction and acute renal failure, respectively. These patients were subsequently treated with radiation alone.

Due to the severity of local reactions a 1 week delay was necessary in nine patients (19%) and 2 weeks in four (8%).

The median total dose of cisplatin actually delivered was 280 mg/m² (87% of the planned dose) (range 160–320 mg/m²). The median total dose of gemcitabine actually delivered was 4600 mg/m² (92% of the planned dose) (range 2500–5000 mg/m²) and the median dose intensity was 450 mg/m²/week (87% of the planned dose intensity); it was >80% in 70% of patients.

All patients who completed the treatment program received 60 Gy of radiotherapy.
Acute toxicity

Forty-three patients were evaluated for acute toxicity. Details of the side-effects and their frequency are reported in Table 3.

Grade III–IV neutropenia and thrombocytopenia were recorded in 44% and 37% of patients, respectively. Five patients (12%) had febrile neutropenia requiring antibiotics and one patient died of sepsis. Despite the 35 patients (81%) that were supported with epoietin α 10 000 IU subcutaneously every other day, starting at hemoglobin levels <10 g/dl—19 (44%) experienced grade III–IV anemia before the end of treatment and most of them were transfused. Four patients (9%) also received a prophylactic transfusion of platelet units.

Eighty-one per cent of patients developed severe mucositis. In 44% of patients oral nutrition was completely impossible. Generally the highest grade of mucosal toxicity appeared during week 5 of treatment. Tube-feeding and/or parenteral nutrition including partial supports were necessary in 40 patients (93%) and almost half of these patients needed hospitalization during the treatment program. Nevertheless, a weight loss ranging between 10% and 20% was recorded in 44% of patients. All these patients, however, recovered to oral nutrition in 4–9 weeks (median, 6 weeks) from the end of combined treatment despite a persistent xerostomia.

Grade II–III cutaneous reactions were observed in 77% of patients.

Activity

According to the protocol rules, response was preliminarily evaluated 1 month after the end of treatment and definitively assessed after 3 months.

Thirty-four patients obtained a CR (72%) and five patients a partial response (11%). Eight patients (17%) were not evaluable for the reasons listed above. Three partial responders with clinically evident residual disease on the neck were rendered disease-free after a radical neck dissection. Thus, the final CR rate was 79% (95% in the evaluable patients).

Events observed at a median follow-up of 38 months are listed in Table 4.

Late toxicity

Seventeen patients, all free from disease at 2-year follow-up, were studied to report treatment-related late effects [21]. Grade II and III xerostomia was observed in five patients and one patient, respectively (29% and 6%). Taste dysfunctions were moderate in four patients (24%) and severe in one.

No severe late effects, such as osteoradionecrosis, mucosal ulceration or necrosis, fibrosis or larynx strictures occurred in any long-term survivors. None needed permanent tube-feeding or gastrostomy.

Discussion

The aim of this trial was to test the feasibility and to explore the activity of an alternating chemo-radiotherapy program including gemcitabine. To our knowledge, only two papers have been published so far on gemcitabine with radiation in head and neck cancer [15, 16].

The only difference between the regimen employed in the present study and the original alternating cisplatin–fluorouracil and radiation regimen first tested at our institute [7] is the use of
gemcitabine, both with cytotoxic and radiosensitizing intent, instead of 5-fluorouracil.

The intention-to-treat CR rate (72%), the actuarial local control (64% at 3 years) and OS achieved (43% at 3 years) are remarkable if we consider that patients enrolled in the present trial had poor-prognosis head and neck cancer. Particularly, 77% of patients had T4 previously untreated, or relapsed after surgery, unresectable disease. We can say that one in every two patients who complete this treatment program is still potentially curable despite the very advanced disease.

**Figure 2.** Overall survival (open circles), progression-free survival (crosses) and loco-regional control (filled circles) on 47 patients.

**Figure 3.** Overall survival (open circles), progression-free survival (crosses) and loco-regional control (filled circles) on evaluable patients.
Moreover, these data favorably compare in terms of activity with those from our database of patients with stage IV disease treated with alternating cisplatin–fluorouracil and radiation within controlled clinical trials (Table 5). In fact, a 30% statistically significant increase in CR rate has been obtained with the gemcitabine-based regimen. This is the difference that we considered satisfactory in the statistical hypothesis. Even long-term local control appears better with this new combined approach (64% versus 40%), although the impact on OS seems to be less significant (43% versus 35%), which may be correlated with the higher incidence of distant failures (metastases and second primaries) observed in the present trial (23% versus 10%). This finding is common to other recent phase II trials testing intensive combined regimens [4, 5]. It is possible that the improved local control achieved by these regimens gave more time to the already existing micrometastases to develop and for second primary tumors to arise. This behavior might support the need to improve the activity of systemic therapy by the use of additional multiagent chemotherapy given before combined treatment and/or the use of biological therapies.

As expected, the inclusion of gemcitabine into an alternating chemoradiation program led to a formidable increase in acute local reactions requiring intensive supportive care in almost the totality of the patients. However, the incidence and severity of late local reactions were acceptable. It was even the case that bone marrow toxicity was significantly increased. In particular, severe anemia was observed in 44% of patients despite the use of epoetin α. Is it possible that, in very aggressive chemo-radiotherapy programs, the administration of this drug at hemoglobin levels <10 g/dl is not adequate. For this reason, in our ongoing chemoradiation programs, we are now considering the administration of epoetin α at hemoglobin levels <12 g/dl.

Eight patients (17%) did not complete the planned therapy program (unevaluable patients) including four patients who died during treatment. The magnitude of this percentage might be considered strictly depending on the intensity of the treatment program. However, we would like to stress that this percentage is comparable with that observed in our experience with the original alternating cisplatin–fluorouracil and radiation program which is an ‘easier’ and less toxic treatment (Table 5). A possible explanation for this finding may be that the characteristics of head and neck cancer patients play a significant role in treatment compliance as well. Most of these patients have concomitant illnesses and they may interrupt the treatment program or die for a number of miscellaneous reasons not necessarily related to the tumor or therapy. Actually, the number of patients who did not complete the planned treatment in our studies is higher than that reported in other phase II trials with aggressive combined programs but, in our opinion, the reason for that should be looked for in a different selection of patients. In fact, in one of the most recently published phase III randomized trials [22], the rate of patients who did not complete the planned treatment in the two chemoradiation arms was even higher (27% and 15%, respectively).

Therefore, despite the preliminary results from phase II studies that seem to encourage aggressive multimodality treatment strategies, in our opinion, the above reported considerations still strongly support the need for adequate phase III studies comparing more aggressive versus less aggressive chemo-radiotherapy programs to definitively assess the role of treatment intensification.

<table>
<thead>
<tr>
<th>Table 5.</th>
<th>Present trial (CDDP/GEM+RT)</th>
<th>IST database (CDDP/5-FU+RT)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Stage IV patients</td>
<td>47</td>
<td>115</td>
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<td>T4, %</td>
<td>77</td>
<td>70</td>
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</tr>
<tr>
<td>Oral cavity, %</td>
<td>11</td>
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<tr>
<td>Oropharynx, %</td>
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<td>Hypolarynx, %</td>
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<td></td>
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<tr>
<td>Grade 3–4 mucositis, %</td>
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<td>Grade 3–4 dermatitis, %</td>
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<td>42</td>
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<tr>
<td>3-year SURV, %</td>
<td>43</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>TTP, %</td>
<td>39</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>LRC, %</td>
<td>64</td>
<td>40</td>
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<tr>
<td>Distant failure, %</td>
<td>23</td>
<td>10</td>
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CDDP, cisplatin; 5-FU, 5-fluorouracil; GEM, gemcitabine; LRC, loco-regional control; SURV, survival; TTP, time-to-progression.
However, to achieve the optimal administration of concomitant chemo-radiotherapy, a high level of experience in this field, as well as the availability of a multidisciplinary team to provide appropriate supportive care, are of crucial importance. In fact, we have recently demonstrated a correlation between treatment institution and outcome [23]. This finding may represent a bias in large multicenter randomized trials, particularly when aggressive strategies are compared to more standard treatments, unless careful selection of the treating institutions is made.

In summary, the inclusion of gemcitabine into an alternating chemo-radiotherapy program, at least in the schedule we tested in this trial, produces formidable acute toxicity, but it is manageable by an experienced team. This more aggressive approach seems to mainly improve locoregional control if compared to the original alternating program. Distant metastases, second primary tumors and comorbidity represented the first cause of death in this trial.

The role of this aggressive combined approach, as well as of others, definitely needs to be addressed in randomized trials.

References