TOXICITY OF TWO CISPLATIN-BASED RADIOCHEMOTHERAPY REGIMENS FOR THE TREATMENT OF PATIENTS WITH STAGE III/IV HEAD AND NECK CANCER

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Abstract: Background. This nonrandomized study compared 2 radiochemotherapy regimens for toxicity in 128 patients with stage III/IV head and neck cancer.

Methods. Patients received conventionally fractionated radiotherapy. The total dose to primary tumor and involved lymph nodes did depend on preceding surgery. Patients received 66 to 70 Gy if surgery was not performed, 60 to 66 Gy after R0 resection, 66 Gy after R1 resection, and 70 to 72 Gy after R2 resection. Concurrent chemotherapy consisted of 3 courses cisplatin (100 mg/m²/d1,22,43) (group A, N = 61) or 2 courses cisplatin (20 mg/m²/d1–5 + 29–33)/5-fluorouracil (5-FU) (600 mg/m²/d1–5 + 29–33) (group B, N = 67).

Results. Acute toxicity was more severe in group A, especially nausea/vomiting (p = .002), nephrotoxicity (p = .001), ototoxicity (p = .034), and hematotoxicity (p = .049). Forty-eight percent of group A and 10% of group B patients could not complete chemotherapy due to toxicity (p = .018). Late toxicity was similar (p = .99).

Conclusion. Two courses of fractionated cisplatin (20 mg/m²/d) and 5-FU were associated with significantly less acute toxicity than were 3 courses cisplatin (100 mg/m²/d). ©2007 Wiley Periodicals, Inc. Head Neck 30: 235–241, 2008

Keywords: head and neck cancer; stage III/IV; radiochemotherapy; cisplatin; toxicity

Locally advanced head and neck cancer carries a poor prognosis. Surgery followed by radiotherapy or radiochemotherapy is the treatment of choice. Several retrospective studies have suggested that postoperative radiotherapy improves locoregional control in patients with head and neck cancer when compared with surgery alone.1–4 The potential benefit of postoperative radiochemotherapy when compared with postoperative radiotherapy alone is still controversial. The Intergroup study 0034 did not demonstrate a significant difference between radiotherapy plus 3 preceding courses of cisplatin/5-fluorouracil (5-FU) chemotherapy and radiotherapy alone with respect to locoregional...
control and overall survival. In the study 95-01 of the Radiation Therapy Oncology Group (RTOG), concurrent chemoradiotherapy with 3 courses of cisplatin was superior to radiotherapy alone for locoregional control, but not for overall survival. The trial 22931 of the European Organization for Research and Treatment of Cancer (EORTC) suggested a benefit for chemoradiotherapy with 3 courses of cisplatin when compared with radiotherapy alone for both estimated 5-year locoregional control and survival. However, the combined approach was associated with a substantial increase in acute toxicity.

Definitive radiotherapy alone or definitive radiochemotherapy are both an option for patients with unresectable disease and serve as an alternative to surgery in appropriate cases. Radiotherapy alone, which had been the standard treatment for patients with unresectable tumors for many years, resulted in survival rates of less than 25% and 2-year locoregional control rates of less than 20%. The treatment outcome may be improved by adding concurrent chemotherapy.

The majority of the available studies comparing radiochemotherapy versus radiotherapy alone for definitive head and neck cancer treatment suggested a survival benefit if concurrent chemotherapy was administered, whereas a few studies did not demonstrate such a benefit. The optimal radiochemotherapy regimen is a matter of debate, because most of the currently used regimens are associated with severe acute toxicity and even treatment-related deaths. Radiochemotherapy with 3 courses of 100 mg/m² cisplatin on days 1, 22, and 43 is the most frequently applied regimen, either as definitive or as adjuvant treatment. However, the acute toxicity of this program is considerable. Marcial et al reported life-threatening renal damage in patients receiving definitive radiochemotherapy. Al-Sarraf et al reported 20% severe toxicities and 12% life-threatening toxicities in patients receiving adjuvant radiochemotherapy with 60 Gy plus 3 courses of 100 mg/m² cisplatin. An alternative radiochemotherapy program associated with less acute toxicity appears desirable.

The vast majority of head and neck cancer studies that included chemotherapy have compared radiotherapy alone versus radiochemotherapy but have not compared different radiochemotherapy schedules. Thus, studies comparing different radiochemotherapy schedules for head and neck cancer treatment are required to determine regimens that provide effective treatment with the least toxicity possible. The present study compares “standard” radiochemotherapy with 3 courses of 100 mg/m² cisplatin on days 1, 22, and 43 to another cisplatin-based chemotherapy regimen consisting of 2 courses of fractionated cisplatin (20 mg/m²/d on days 1–5 and 29–33) and 5-fluorouracil (600 mg/m²/d on days 1–5 and 29–33) with respect to toxicity in the treatment of locally advanced head and neck cancer.

**MATERIALS AND METHODS**

**Patients.** Between January 1998 and January 2006, 128 patients with stage III/IV carcinoma of the head and neck (17 nasopharynx, 48 oropharynx, 34 oral cavity, 16 hypopharynx, 13 larynx) received concurrent radiochemotherapy, either as definitive or as adjuvant treatment. Criteria for inclusion in this retrospective study were as follows: histologically proven carcinoma arising from the nasopharynx, the oropharynx, the oral cavity, the hypopharynx, or the larynx, and tumor stage III or IV according to the American Joint Committee of Cancer (AJCC) criteria based on CT and direct examination with endoscopy. According to the administered chemotherapy regimen, the patients were divided in 2 groups (see section Chemotherapy). The treatment regimen was mainly related to interdisciplinary (study) protocols being favored at the institutions at certain periods of time. These protocols varied due to the controversy in determining the best treatment for locally advanced head and neck cancer. Each series of patients from the contributing centers represents a series of patients treated with a specific regimen over a certain period of time. Group A consisted of 61 patients who came from Hamburg (N = 27, 2003–2004 and 2006), Sarajewo (N = 24, 2003–2005), Luebeck (N = 6, 1999–2000), and Tilburg (N = 4, 2003–2004); Group B consisted of 67 patients who came from Hamburg (N = 67, 1998–2003 and 2004–2006). In addition to the investigators from the participating centers, the principal investigator reviewed the patient files in order to assure that there was no relevant variation of treatment factors, which might have introduced a selection bias. The patient characteristics related to the 2 treatment groups are listed in Table 1. These patients have not been reported elsewhere.

**Chemotherapy.** Group A (n = 61): The concurrent chemotherapy consisted of cisplatin, which was
administered intravenously at a dose of 100 mg/m² of body-surface area on days 1, 22, and 43 of the course of radiotherapy. The patients received 1500 mL of hydration given over 90 minutes before administration of cisplatin plus 20 to 40 mg of furosemide, and mostly 4 to 8 mg of ondansetron. Cisplatin was administered over 1500 mL of hydration. The chemotherapy was administered by the radiation oncologists. The median cumulative cisplatin dose administered in group A patients was 300 mg/m² (range, 100–300 mg/m²) of body-surface area.

Group B (n = 67): The concurrent chemotherapy consisted of cisplatin administered intravenously at a dose of 20 mg/m² of body-surface area on days 1 to 5 and 29 to 33 of the course of radiotherapy, as well as of 5-fluorouracil (5-FU) administered intravenously as a continuous infusion for 120 hours at a daily dose of 600 mg/m² of body-surface area on days 1 to 5 and 29 to 33 of the course of radiotherapy. On each day of cisplatin administration, the patients received 1000 mL of hydration given over 60 minutes before administration of cisplatin plus 20 to 40 mg of furosemide, and mostly 4 to 8 mg of ondansetron. Cisplatin was administered over 30 minutes, followed by another 1000 mL of hydration. Also in this group, the chemotherapy was administered by the radiation oncologists.

The median cumulative cisplatin dose administered in group B patients was 200 mg/m² (range, 100–200 mg/m²) of body-surface area.

**Radiotherapy.** All patients received conventionally fractionated radiotherapy (5 fractions per week) with doses per fraction of 2.0 Gy. Maximal and minimal target-volume doses and the maximal dose delivered to the spinal cord were recorded. Radiotherapy was performed with a linear accelerator and 4 to 6 megavoltage (MV) photons, as well as 10 to 12 MV electrons for parts of the posterior cervical lymph nodes, to limit the dose to the spinal cord to 45 Gy. The total dose delivered to the primary tumor and to the involved lymph nodes (according to CT) depended on preceding surgery. The total doses and the extent of resection related to the 2 treatment groups A and B are summarized in Table 2. The total dose to the other cervical and supraclavicular lymph nodes was 50 to 60 Gy. The total radiation doses also depended on interdisciplinary (study) protocols favored at the various treating institutions.

**Study Endpoints, Follow-Up, and Statistics.** Both treatment groups were compared for acute and late toxicity. Acute toxicity was evaluated according to the Common Toxicity Criteria (CTC version 2.0), and late toxicity according to the RTOG criteria. Late toxicity was defined as toxicity occurring later than 90 days after radiochemotherapy was started.

During radiotherapy the patients were prospectively and consistently followed for toxicity once a week, and after radiotherapy the patients were followed at regular intervals (usually every...
3–6 months) or until death. The median follow-up was 12 months (range, 0–66 months) in the entire cohort, 13 months (range, 0–66 months) in group A, and 11 months (range, 0–66 months) in group B. The relatively short follow-up is a reflection of early analysis rather than of low overall survival.

Uncompleted chemotherapy was defined either as not all planned chemotherapy courses given or as a dose reduction of at least 25% during 1 or 2 courses. Patient characteristics and toxicity were compared with the chi-square test.

**RESULTS**

Significantly \((p = .018)\) more group A patients (29/61, 48%) could not complete the chemotherapy due to acute toxicity than group B patients (7/67, 10%). In group A, 14 patients received only 1 course of chemotherapy (100 mg/m² of cisplatin; 33% of the prescribed cumulative dose), and another 14 patients received only 2 courses of cisplatin (200 mg² of cisplatin; 67% of the prescribed cumulative dose). One patient received 1 complete course and 1 course with a 25% dose reduction (175 mg² of cisplatin; 58% of the prescribed cumulative dose). In group B, 4 patients received only 1 course of chemotherapy (100 mg/m² of cisplatin; 50% of the prescribed cumulative dose), and 3 patients received 1 complete course of chemotherapy plus 1, 2, and 3 days of the second course, respectively (120, 140, and 160 mg/m² of cisplatin; 60%, 70%, and 80% of the prescribed cumulative dose).

Of the 29 group A patients who did not complete the chemotherapy, 8 patients received only 60 Gy of irradiation (after R0 resection). In these 8 patients, only 2 courses of 100 mg/m² cisplatin were planned. However, the patients experienced serious acute toxicity after the first course (grade 3–4 hematotoxicity in 5 patients, grade 2 nephrotoxicity in 3 patients, grade 3 vomiting in 3 patients, grade 2 ototoxicity in 1 patient), and the second course cisplatin was either not administered or given with a dose reduction of at least 25%.

Additionally, significantly more group A patients developed at least 1 grade 3–4 toxicity considered to be chemotherapy induced (59% vs 21%, \(p = .003)\), such as nephrotoxicity, ototoxicity, nausea/vomiting, hematotoxicity, and treatment-related death due to pneumonia or sepsis following neutropenia (Figure 1). Due to the fact that the antiemetic regimen may be considered less than the standard treatment in many other centers worldwide, the toxicity rates were recalculated without nausea/vomiting. Again, significantly more group A patients developed at least one grade 3–4 toxicity considered to be chemotherapy induced (48% vs 18%, \(p = .005)\).

The acute toxicity most likely radiotherapy induced, such as mucositis, skin toxicity within the radiation fields, and xerostomia, was comparable in both treatment groups (Figure 1). Late toxicity such as late xerostomia, late skin toxicity, cervical fibrosis, and cervical lymph edema was similar in both groups (Figure 2). Seven percent of the group A patients and 10% of the group B patients developed grade 3 late xerostomia, and 7% (group A) and 13% (group B) developed cervical fibrosis. No grade 4 late toxicity was observed.

According to the Kaplan–Meier analyses\(^{24}\) for the entire cohort, the 2-year rate of locoregional control was 70%, the 2-year rate of metastasis-free survival was 69%, and the 2-year rate of overall survival was 63%, respectively. The 2-year locoregional control rates were 72% for group A patients and 66% for group B patients \((p = .32)\). The 2-year metastasis-free survival rates were 77% and 68%, respectively \((p = .92)\), and the 2-year survival rates were 68% and 56%, respectively \((p = .82)\).

**DISCUSSION**

Very few reports have compared various radiochemotherapy regimens for locally advanced head and neck cancer. The present study compared 2 different radiochemotherapy programs (group A: 3 courses of 100 mg cisplatin alone on days 1, 22,
43 vs group B: 2 courses of 20 mg/m² cisplatin/600 mg/m² 5-FU on days 1–5 and 29–33). However, one has to be aware of the limitations of the study presented here. The retrospective nature of the study and the heterogeneity of the patients should be taken into account when interpreting this analysis. The patient population included those treated with definitive chemoradiotherapy alone as well as postoperative patients with R0, R1, and R2 resections. Thus, a selection bias may have been introduced.

The radiochemotherapy schedule administered in group A was associated with significantly more acute toxicity than the schedule administered in group B, especially in terms of nephrotoxicity, hematotoxicity, and nausea/vomiting. This may be explained by the fact that group A patients received more cisplatin than group B patients. Adding 5-FU was tolerated in group B patients, because they received less cisplatin and because cisplatin was fractionated. Fractionated administration of cisplatin (20 mg/m²/day for 5 days) may
be considered less toxic than a single dose of 100 mg/m² given in 1 day. Only 52% of the group A patients was able to receive the complete chemotherapy as initially planned, whereas the other 48% of the patients developed severe chemotherapy-related acute toxicity, which did not allow the administration of the complete chemotherapy. In the series of Forastiere et al, who treated patients with laryngeal cancer for organ preservation, the rate of high-grade toxic effects was greater with the chemotherapy-based regimens (81% with induction cisplatin/5-FU followed by radiotherapy and 82% with radiotherapy plus 3 courses of concurrent cisplatin) than with radiotherapy alone (66%). Seventy percent of the patients who received concurrent chemotherapy arms could receive all 3 courses of 100 mg/m² cisplatin. This rate may be higher than in our series, because the authors did not consider patients who needed a reduction of the chemotherapy dose. In our study, both cessation of chemotherapy and dose reductions were considered as uncompleted chemotherapy.

The randomized RTOG 97-03 study compared 3 different radiochemotherapy regimens for toxicity and outcome in 241 patients with squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx. The patients received either 70 Gy given in 7 weeks with 10 mg/m² cisplatin and 400 mg/m² of 5-FU daily during the last 10 days of radiotherapy (arm 1), 70 Gy in 13 weeks (given on alternating weeks) with daily hydroxyurea (1 g BID) and 800 mg/m² of 5-FU (arm 2), or 70 Gy in 7 weeks with weekly paclitaxel (30 mg/m²) and cisplatin (20 mg/m²) (arm 3). Ninety-two percent, 79%, and 83% of patients on arms 1, 2, and 3, respectively, were able to complete their radiation as planned or with an acceptable variation. Fewer than 10% of patients had unacceptable deviations or incomplete chemotherapy in the 3 arms. Estimated 2-year disease-free and overall survival rates were 38.2% and 57.4% for arm 1, 48.6% and 69.4% for arm 2, and 51.3% and 66.6% for arm 3. The grade 4 toxicity rates were similar in the 3 groups, being 18%, 29%, and 23%, respectively. There were 3 deaths (4%) attributed to treatment toxicity in arm 1. All 3 deaths occurred subsequent to the chemotherapy delivery. Four and 5 patients died during or within 30 days of completion of their therapy on arms 2 and 3, respectively. The rates of treatment-related deaths are comparable to the 4% of our group A patients, but higher than the 1% of our group B patients.

The acute toxicity that was likely related to radiotherapy, such as mucositis, skin toxicity, and xerostomia, did not significantly differ between the 2 groups. The late toxicity such as late xerostomia, late skin toxicity, cervical fibrosis, and cervical lymph edema was similar in both groups. Xerostomia and cervical fibrosis rates in our series (7% to 10% and 7% to 13%, respectively) were comparable to those of other schedules as reported by Calais et al, who treated patients with advanced-stage oropharynx carcinoma with definitive concurrent radiochemotherapy including 3 courses of a 4-day regimen of 70 mg/m² carboplatin and 600 mg/m² 5-FU. They reported 9% grade 3–4 xerostomia and 11% grade 3–4 cervical fibrosis.

In conclusion, for radiochemotherapy of stage III/IV head and neck cancer, the regimen including 2 courses of fractionated cisplatin (20 mg/m²/d on radiotherapy days 1–5 and 29–33) and 5-FU (600 mg/m²/d on radiotherapy days 1–5 and 29–33) was associated with significantly less acute toxicity than 3 courses of cisplatin (100 mg/m² on radiotherapy days 1, 22, and 43). Adding 5-FU was tolerated by group B patients, because these patients received less cisplatin and because cisplatin was fractionated. The results of this retrospective study need to be confirmed in a randomized trial.

REFERENCES


