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CLINICAL INVESTIGATION **Head and Neck**

RADIOCHEMOTHERAPY WITH CETUXIMAB, CISPLATIN, AND AMIFOSTINE FOR LOCALLY ADVANCED HEAD AND NECK CANCER: A FEASIBILITY STUDY

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Purpose: Radiotherapy (RT) combined with cisplatin or cetuximab is the standard of care for patients with locally advanced head/neck cancer (LA-HNC). The feasibility of radiochemotherapy with cisplatin and cetuximab, supported with amifostine, was herein investigated.

Methods and Materials: Forty-three patients with LA-HNC were recruited. Conformal hypofractionated/accelerated RT with amifostine cytoprotection (2.7 Gy/fraction, 21 fractions in 4 weeks) was combined with cisplatin (30 mg/m^2/week) and cetuximab (standard weekly regimen) therapy. The dose of amifostine was individualized according to tolerance.

Results: A high daily amifostine dose (750–1,000 mg) was tolerated by 41.8% of patients, and a standard dose (500 mg) was tolerated by 34.9% of patients. A high amifostine dose was linked to reduced RT delays ($p = 0.0003$). Grade 3 to 4 (3-4) mucositis occurred in 7/43 (16.2%) patients, and fungal infections occurred in 18/43 (41.8%) patients. Radiation dermatitis was not aggravated. Interruption of cetuximab due to acneiform rash was necessary in 23.3% of patients, while amifostine-related fever and rash were not observed. Severe late radiation sequelae consisted of laryngeal edema (9% laryngeal cases) and cervical strictures (33% of hypopharyngeal cases). Good salivary function was preserved in 6/11 (54.5%) nasopharyngeal cancer patients. The complete response rate was 68.5%, reaching 77.2% in patients with minor radiotherapy delays. The 24-month local control and survival rates were 72.3% and 91%, respectively (median follow-up was 13 months.).

Conclusions: In this feasibility study, weekly administration of cisplatin and cetuximab was safely combined with accelerated RT, supported with amifostine, at the cost of a high incidence of acneiform rash but a reduced incidence of amifostine-related fever/rash. A high daily dose of amifostine allows completion of therapy with minor delays. © 2010 Elsevier Inc.

Radiotherapy, Acceleration, Cetuximab, Cisplatin, Amifostine.

INTRODUCTION

About 400,000 head/neck squamous cell carcinomas are diagnosed worldwide annually, most of which are locally advanced at presentation (1). This latter group of patients will require multimodal treatment with RT and cisplatin chemotherapy (2). Meta-analysis clearly supports concomitant radiochemotherapy (3, 4). The meta-analysis by Pignon *et al*. demonstrated that the addition of chemotherapy to radiation improved 5-year overall survival by 5%, with patients receiving concomitant chemotherapy showing a survival benefit of 8% at 5 years (3). In the Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck (MARCH) study (5), altered fractionation improved survival by 3.4% at 5 years. However, it must be underlined that among patients treated with accelerated radiation with dose reduction, survival was nonsignificantly improved by only 1.7% (5). In individual randomized radiochemotherapy studies, an estimated 10% benefit in terms of local control and overall survival has been suggested by most of the studies. Reduction of the overall treatment time by 1 to 2 weeks by using acceleration techniques (6, 7, 8) or by increasing the total dose using hyperfractionation (7, 9) showed, similar to results achieved by radiochemotherapy, a 10% benefit over standard radiotherapy. However, these studies do not have the statistical power of the previously mentioned meta-analyses, and one can conclude a clear benefit of 3 to 5 % for both fields of clinical research, which are encouraging. It is expected that altered fractionation will provide even better

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results if combined with chemotherapy, as indeed confirmed in a study by Brizel *et al* (10).

The dominant position of cisplatin in concurrent radiochemotherapy schedules for head and neck cancer (HNC) has been recently challenged by a randomized study of anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (cetuximab [Erbitux]) administration during standard radiotherapy (11). The addition of cetuximab increased the median survival by 20 months without increasing the radiation toxicity, with the common undesirable effect being an acneiform rash. That study allowed the approval of cetuximab as the first-line drug combination with RT in HNC patients. In a more recent study, the addition of cetuximab to platinum-based chemotherapy improved the response rates and survival of HNC patients with metastatic or recurrent disease, with the cost of more frequent sepsis and skin reactions (12). The combination of RT with both platinum and cetuximab seems, therefore, a reasonable step in the chase of more effective regimens for locally advanced HNC.

In the present study we investigated the feasibility of cisplatin, cetuximab, and accelerated RT, supported with an individualized daily dose of amifostine, a cytoprotective drug approved for protection against radiation xerostomia (13).

METHODS AND MATERIALS

Patients with locally advanced tumors of HNC (LA-HNC) were recruited in a prospective phase II study to investigate the tolerance and efficacy of conformal hypofractionated/accelerated radiotherapy with cytoprotection (HypoARC), using daily administration of individualized doses of amifostine concurrently with weekly administration of cisplatin and cetuximab anti-EGFR monoclonal antibody. The radiotherapy-chemotherapy regimen has been previously reported by our group (14).

Thirty-seven of these patients had tumors that were inoperable, while 6/43 patients had undergone surgical incomplete resection with histologically confirmed or gross residual disease. Criteria for inoperable cases were cancer of the nasopharynx, disease extension T4b, with or without lymph node involvement or large lymph nodes of the neck, as well as medical reasons, according to the NCCN Practice Guidelines in Oncology version 2.2008 (1). In brief, a tumor was characterized as unresectable if the institution's surgeons considered radical removal of the tumor impossible without major functional impairments.

Inclusion criteria consisted of patients older than 18 years, a good performance status, as well as a normal hematological and biochemical blood status at the time of entry into the study. Only patients with carcinomas (including salivary gland carcinomas) entered the study. Other criteria were medical suitability for definitive radiotherapy and no previous chemotherapy or radiotherapy within the last 3 years. Patients with hypopharyngeal/oropharyngeal tumors with total aphagia were also excluded, as no feeding tubes were allowed, so treatment delays were an objective measure of the severity and duration of toxicity. All patients gave written informed consent, and the study was approved by the Ethics and Scientific committee of the University Hospital of Alexandroupolis (approval number DS PGNA SD 34/2006).

Staging evaluation included a thorough clinical examination performed by a head and neck specialist (including an endoscopic examination), computed tomography (CT) or magnetic resonance imaging scans of the head and neck, CT scans of the thorax and upper abdomen, as well as hematological evaluation (complete blood cell count and biochemical tests) of the patient. Positron emission tomography (PET) or PET/CT scans were not routinely performed.

Table 1. Tumor characteristics

Disease site and stage	No. of patients
Nasopharynx	11
T1, T2-N2, N3	5
T3-N0	2
T4-N0, N1, N2	4
Larynx	9
T3-N0, N1	2
T3-N2	1
T4-N0, N1	6
Epilarynx	2
T2 – N0, N1	2
Oropharynx	6
T2-N0, N1	3
T3-N0, N1	2
T2-N3	1
Hypopharynx	5
T2,3-N0, N1	3
T4-N0, N1, N2	2
Neck	3
Tx-N3	3
Parotid	4
T2, T3, T4-N0, N1	4
Skin	3
T4-N0, N1, N2, N3	3
Total	43

Disease characteristics are listed in Table 1. All patients had a good performance status (0–1; median, 0). Eleven patients were female, and 22 patients were male. The median age was 66 years (range, 36–87 years). The median follow-up was 13 months (2–35 months), and for living patients a minimum follow-up of 6 months was available.

RT details

RT was given using a 6- or 18-MV linear accelerator with a multileaf collimator after CT simulation and conformal radiotherapy planning (Plato, Nucletron). Large daily fractions of 2.7 Gy were used for 14 fractions before changing fields to shield the spinal cord and deliver one additional fraction to the upper neck. After that, an individualized booster dose to the CT-detectable tumor and involved nodes was planned. This booster dose was given, again, with 2.7-Gy fractions to a total of 21 fractions (physical dose of 56.7 Gy). The lower neck/supraclavicular area was also irradiated through an anterior field, receiving 15 fractions of 2.7 Gy in 15 days (physical dose of 40.5 Gy). Involved nodal areas received a higher dose (17–20 fractions). The plan was to deliver 21 radiotherapy fractions (56.7 Gy) without a split, if feasible, within 29 days.

Gross tumor volume, clinical target volume (CTV), and planning target volume were delineated according to the disease site and respective principles. A 1- to 2-cm margin was used for planning target volume delineation around the gross disease at presentation for the boost field to allow for setup errors. The range of doses given to nodal disease was determined by tumor location, tumor size ($\pm$5 cm), and response. The decision was mainly clinical. The maximal dose to the spinal cord was the biologically equivalent dose of

<44 Gy, and the maximum dose allowed to the mandible was 50 Gy. The parotid dose in nasopharyngeal cases was recorded and ranged from 40 to 50 Gy. Finally, the allowable percent inhomogeneity (both maximum and minimum) within the target volume was ±5% (delivered to ≥95% of the CTV).

In order to translate the above-cited physical dose to its biological equivalent dose, we calculated the normalized total dose (NTD) by using the formula proposed by Maciejewski and Maciejewski (15): $NTD = D\ [(\alpha/\beta + d)/(\alpha/\beta + 2)]$, where D is the total physical dose, d is the dose per fraction, and α/β is the tissue-specific ratio. The NTD corrected for overall treatment time $NTD_{(T)}$ was calculated using a previously proposed formula (16): $NTD_{(T)} = D\ [(\alpha/\beta + d)/(\alpha/\beta + 2)] + \lambda(Tc - To)$, where Tc is the number of days required for the delivery of the NTD, using a conventionally fractionated scheme (2 Gy/fraction), To is the number of days required for the delivery of the current scheme, and λ is the estimated daily dose consumed to compensate for rapid tumor repopulation. For cancer tissue, an α/β ratio range from 4 to 10 Gy was considered. We also assumed a median λ value range for cancer cells of 0.4 to 0.8 Gy (15, 16). For normal tissues, an α/β ratio of 4 Gy and a λ value of 0.2 were considered.

Using the above assumptions, the NTD delivered to the normal tissues was 63.3 Gy, and the respective dose to the tumor ranged from 60 to 63.3 Gy. This dose was given within 29 days instead of 44 days, as required to deliver this dose by conventional fractionation (2 Gy/fraction), so that a 15-day acceleration of therapy was exploited. Taking into account the above mentioned λ values, the NTD for normal tissues (in the area of booster dose) was 66.3 Gy and for the tumor 66 to 75.3 Gy.

Amifostine administration and dose individualization

Amifostine, 1,000 mg, was diluted in 5 ml of water for injection and was injected at two sites (usually in the right and left shoulders). RT followed within 20 to 30 minutes. The dose of 1,000 mg was reached gradually by starting at 500 mg and increasing the dose by 250 mg/day. In this way, the optimal tolerable dose for each patient was identified (17). Generalized rash or fever attributed to amifostine was followed by immediate interruption of amifostine and oral administration of corticosteroids and antihistamines for 3 days (18).

Concurrent and post-RT chemotherapy

Patients received cisplatin, 30 mg/m^2, weekly and cetuximab, 400 mg/m^2 for week 1 and 250 mg/m^2 weekly thereafter, for a total of 5 weeks. Administration of chemotherapy started on day 1 of radiotherapy. Patients with good tolerance to the radiochemotherapy phase (mucositis grade ≤2, acneiform rash grade ≤1, fatigue grade ≤1) received further chemotherapy for four consecutive cycles of cisplatin (60 mg/m^2) and cetuximab (500 mg/m^2) every 2 weeks.

Treatment evaluation

Complete blood cell count, serum urea, creatinine, and liver enzymes were assessed once per week during the radiochemotherapy period. Radiation toxicity was monitored daily during RT, weekly for 1 month following the end of RT, monthly for 4 months, and every 3 months thereafter. The National Cancer Institute Common Toxicity Criteria version 2 scale (www.fda.gov/cder/cancer/toxicityframe.htm) was used to assess chemotherapy and acute radiation toxicity. The RTOG protocol 0522 head and neck adverse event grading tool version 3.0 was used to grade late toxicities and the cetuximab-related rash (www.rtog.org/members/protocols/0522/AEGradingTool.html). Response to treatment of measurable lesions was assessed with CT scans obtained at 2 and 4 months after treatment completion.

Patient support during therapy

Grade 3 to 4 (3-4) mucositis and/or severe fungal infections preventing adequate nutrition or other nonhematological toxicities were followed by treatment delay for as many days required for the patient to recover and for feeding with semiliquid food to become feasible again. No feeding tubes (nasogastric or percutaneous) were used before therapy. Fungal oral/oropharyngeal infections were initially treated with oral administration of mycostatin, and when the patient was resistant, with pozaconazole (Noxafil), 200 mg, four times per day, until the end of RT.

Neutropenia grade 1-2 was prophylactically treated with pegfilgrastim. Nonfebrile neutropenia grade 3-4 was followed by an immediate administration of pegfilgrastim and a 1 week's delay of chemotherapy administration. Low hemoglobin levels or a drop in hemoglobin to below 11.5 gm/dl% was treated with erythropoietin. Patients with hemoglobin of <10 gr% at presentation were treated with red blood cell transfusion and erythropoietin support before the onset of therapy. Grade 3-4 platelet toxicity was followed by omission of cisplatin until the patient recovered to grade ≤2.

Cetuximab-related acneiform rash was treated with oral doxycycline (100 mg per day) and local application of clindamycin C solution. Grades 2 and 3 rash was followed by permanent interruption of cetuximab and continuation of radiotherapy with cisplatin alone. These presumably stricter criteria (compared to the study by Bonner *et al.* [11]) for cetuximab discontinuation were included in the protocol due to an anticipated increased skin toxicity (combination of cetuximab with amifostine) but also because a previous pilot study experience with cetuximab showed high rates of rash progression that compromises the flow of radiotherapy if cetuximab was administered after grade 2 rash appearance. In any case, in our experience, the description of acneiform rash by the available grading scales is rather rough, so the borders between grade 2 and 3 rash are difficult to distinguish. Briefly, extensive rash to the face and upper trunk, with evident disfigurement and/or intense burning sensation were the criteria to permanently interrupt cetuximab.

Statistical analysis

Statistical analysis was performed and graphs were constructed using GraphPad Prism version 4.0 software. Fisher's exact test was used for testing relationships between categorical variables. Survival and locoregional control (time to locoregional disease progression following tumor regression calculated from the time of entry to the study) curves were plotted using the Kaplan–Meier method. Two-tailed p values are given. A p value of <0.05 was considered statistically significant.

RESULTS

Amifostine dose and tolerance

Fourteen (32.5%) patients received a daily dose of 1,000 mg of amifostine. Four (9.3%) patients tolerated a daily dose of 750 mg well, and 15 (34.9%) patients tolerated a dose of 500 mg. At this individualized dose level, patients tolerated amifostine without any side effects or with mild nausea and/or fatigue. Ten (23.3%) patients did not tolerate the 500-mg dose, and amifostine was interrupted at some point during therapy (after 3–6 days). None of the patients developed

Table 2. Early radiation toxicity in 43 patients with locally advanced HNC treated with HypoARC, according to the amifostine dose level

	Mucositis grade	Fungal infection	Skin grade	RT delay period (weeks [w])
Amifostine dose level (mg/m^2)	1 2 3-4	No Yes	1 2 3-4	None <1w 1-2w >2w
0 (10 patients)	1 7 2	5 5	8 1 1	3 2 2 3
500 (15 patients)	6 5 4	9 6	12 3 0	4 1 8 2
≥750 (18pts)	8 9 1	11 7	16 2 0	13 4 1 0
p value	0.10*	0.83	0.23†	0.0003‡

* Grade 3-4 vs. 1-2.
† 0-500 mg vs. ≥750 mg.
‡ Delays of >1 week (w) in the 0-500 mg vs. the ≥750mg group.

fever/rash symptoms, in contrast to the higher than 10% incidence in previous series. Extensive local erythema at the site of injection appeared in 4/43 patients, and these were treated with local steroids.

Early radiation toxicity

Table 2 shows the early toxicity and RT delays in patients treated with HypoARC, according to the amifostine dose level. Patients receiving 750 to 1,000 mg of amifostine experienced a lower incidence of grade 3-4 mucositis (1/18 vs. 6/25 patients), but the difference did not reach significance ($p = 0.10$). The fungal infection was common in all groups. Focal moist skin desquamation was infrequent, and although the incidence was much lower at the 750 to 1,000 mg dose level (2/18 vs. 5/25 patients), this was not statistically significant ($p = 0.23$). A significant association of high amifostine dose with reduced incidence of delays was noted, as only 1/18 patients in the high-dose amifostine group had to delay radiotherapy for more than 1 week vs. 15/25 patients who received 0 to 500 mg of amifostine ($p = 0.0003$). Two patients required hospitalization for fluid administration, but none demanded feeding tube placement due to protracted aphagia during treatment.

Chemotherapy toxicity

Cetuximab-related acneiform rash was the main side effect of chemotherapy. Grade 2 extensive rash of the face and upper trunk demanding medical therapy was noted in 9/43 (20.9%) patients, while grade 3 rash with extensive desquamation, pain, and disfigurement was noted in 1/43 (2.3%) patients (combined grade 2 and 3, 10/43 [23.3%] patients). For all these patients, cetuximab was permanently interrupted and chemotherapy was continued with cisplatin alone. Severe acneiform rash appeared in 2/10 patients following the first administration of cetuximab, in 3/10 patients following the second administration, and in 5/10 patients following the third administration. Acneiform rash regressed within 3 to 5 weeks in patients with grade 2 rash but required more than 2 months to regress in 1 patient with grade 3 acne.

Nonfebrile grade 3 neutropenia appeared in 1/43 (2.3%) patients, and grade 2 neutropenia appeared in 9/43 (20.9%) patients. Neutrophil counts were rapidly restored within 1 to 2 days after pegfilgrastim administration. Thrombocytopenia grade 3 was noted in 1/43 (2.3%) patients, and cisplatin was delayed by 1 week.

Table 3. Response rate according to delays of radiotherapy

	No. of patients (% of total)			
Response	No delay	<1week delay	1-2 weeks delay	>2 weeks delay
All	15	7	8	5
CR	11 (73.4)	6 (85.7)	6 (75)	1 (20)
PR	2 (13.33)	1 (14.3)	2 (25)	3 (60)
SD	2 (13.33)	0	0	1 (20)

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.

Late radiation toxicity

Within a median follow-up period of 13 months (6–35 months), patients treated with HypoARC showed an acceptable incidence of late sequelae. Out of 11 patients treated for laryngeal/epilaryngeal cancer, 1 (9%) patient developed laryngeal edema grade 4 (diffuse laryngeal edema with narrowing of the airway by >50%). Two out of 6 (33%) patients with hypopharyngeal cancer developed grade 3 cervical stricture. Fibrosis grade 2 of neck tissues was noted in 4/43 (9.3%) cases. No tissue necrosis was noted. Good salivary function was preserved in 6/11 patients with nasopharyngeal cancer (grades 0, 1), while grade 2 xerostomia with significant oral intake alteration was noted in the remaining 5/11 patients.

Response rates: survival

Thirty-five patients were evaluable for response assessment with CT (6 had undergone surgery and 2 were lost to follow-up). Complete response was noted in 24/35 (68.57%) patients, partial response in 8/35 (22.85%) patients, and stable disease in 3/35 (8.58%) patients. The response rate according to the delays of RT is shown in Table 3. Radiotherapy delays beyond 2 weeks were linked with significantly poorer CR rates (1/5 vs. 23/29 patients; $p = 0.03$).

The local progression-free interval and overall survival rates are shown in Fig. 1. The 24-month local relapse-free survival rate was 72.3%, while the 24-month overall survival rate was 91%. Three patients relapsed to distant organs (6.9%), two of them with local disease progression.

DISCUSSION

Various RT regimens exploit different tumor or normal tissue responses to the dose per fraction applied and to the overall treatment time, aiming to increase efficacy. The theoretical advantage of each one, however, is compromised by

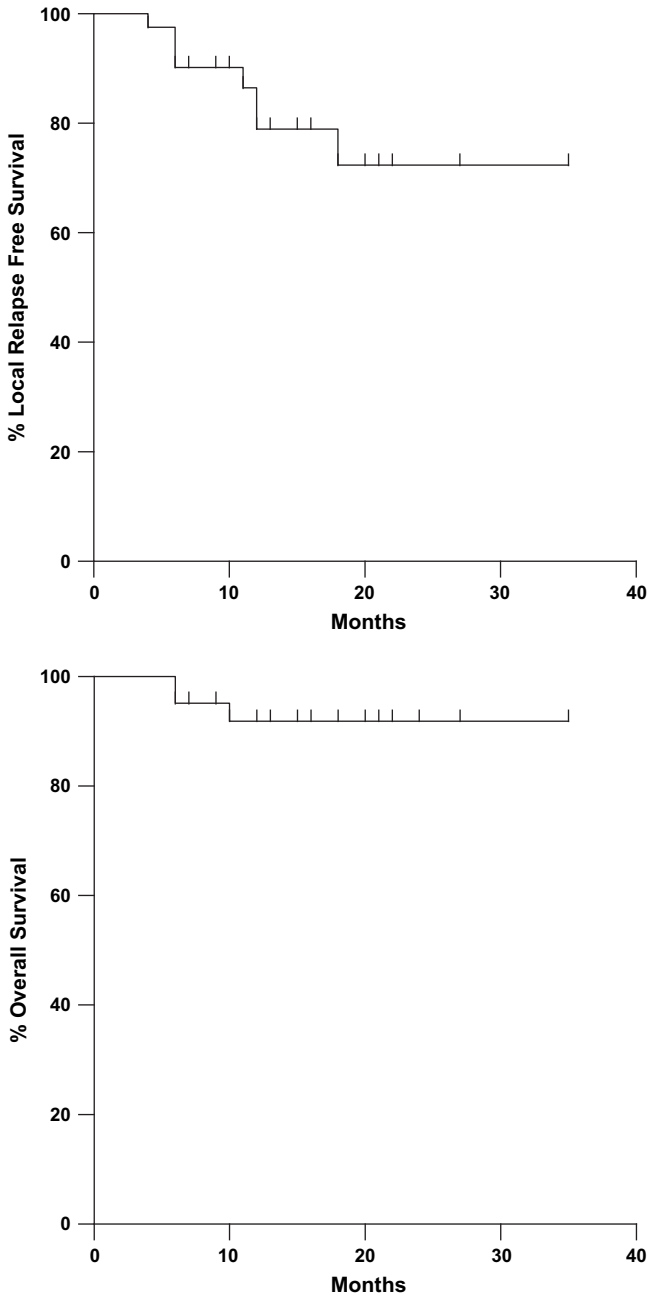

Fig. 1. Kaplan-Meier survival curves showing local progression-free survival (top panel) and overall disease-specific survival (bottom panel).

disadvantages. Indeed, the lack of methods to group tumors according to their specific intrinsic radiosensitivity (*e.g.*, high or low tumor α/β ratio) or to calculate the magnitude of accelerated repopulation during RT lead inevitably to trials with inhomogeneous groups of tumors. Documentation of superiority of one regimen over the other depends mainly on the composition of the treated group. A high percentage of tumors responding better to a particular regimen guarantees detection of statistical benefits, but such studies provide no clue as to whether the failures of the tested arm could have responded better to the RT schedule of the control arm.

The addition of targeted therapies to different radiotherapy schedules may further enhance the efficacy of the latter by increasing sensitivity of subgroups of tumors that would otherwise be resistant to the schedule applied. An interesting paradigm for the above-described hypothesis comes from a translational analysis of the DAHANCA study, where head-neck tumors with EGFR overexpression benefited the most from RT acceleration (19), suggesting that an active EGFR signal transduction system is a major indication for accelerated radiotherapy schedules. Another important paradigm is a translational report in the CHART trial, where conventional and hyperfractionated/accelerated radiotherapies were equally inadequate to locally control tumors with active hypoxia pathways (20). Hypofractionation may be necessary in such tumors (14). In any case, addition of agents targeting such pathways is expected to improve the efficacy of RT, as indeed confirmed by adding cetuximab to standard RT (11).

In the present study we chose a hypofractionated accelerated scheme of RT, which in theory provides better targeting of tumors with relatively low α/β ratios, such as hypoxic tumors and tumors with high repopulation ability. The expected increased early toxicity of such an accelerated regimen was confirmed in 25 patients receiving no or low-dose amifostine, 30% and 13% of whom had to interrupt therapy for more than 2 weeks, respectively, before mucositis regressed to acceptable levels. Only minor delays were required when the daily dose of amifostine was 750 to 1,000 mg. Thus, high dose amifostine contributed to the faster recovery of early toxicities. Delays for more than 2 weeks seemed to have an important impact on the outcome of therapy.

The addition of cetuximab to the standard weekly cisplatin radiochemotherapy did not aggravate early toxicities. In direct contrast to the study by Bonner *et al.* (11), a recent EORTC survey reported a 49% incidence of grade 3-4 radiation dermatitis (21). In a report by Pryor *et al.*, the grade 3-4 skin toxicity was as high as 77% (22). In our study, grade 3-4 skin toxicity was only seen in 1/10 (10%) patients receiving no amifostine, while no such toxicity was noted in patients treated with amifostine. In a pilot study of 22 patients treated with cisplatin, cetuximab, and RT by Pfister *et al.* (23), the grade 3-4 skin toxicity rate was 20%. The grade 3-4 mucositis rate was 38%, which although acceptable, is higher than that noted in our study. The above-mentioned study was interrupted prematurely due to deaths from pneumonia, myocardial infarction, and bacteremia. Such important adverse events were not recorded in our study, despite the RT acceleration. The different cisplatin schedule used in the study by Pfister *et al.* (23) (100 mg/m^2 every 3 weeks) may have accounted for these unacceptable toxicities. In our study, weekly cisplatin (30 mg/m^2) administration was not linked with this type of lethal side effect.

The main side effect from the addition of cetuximab was the acneiform rash, which was severe and demanded permanent interruption of cetuximab after 1 to 3 cycles in about 25% of cases. This rate is in the range of incidence reported by Bonner *et al.* (10) and Pfister *et al.* (22). With the exception of one worrisome case of a young female patient, acneiform rash regressed within 3 to 5 weeks after cetuximab

interruption and proper medication. An interesting finding of the present study was the compatibility of cetuximab with amifostine. Amifostine fever/rash symptoms typically occur in about 10 to 15% of patients (18), and one might expect an increase in the frequency and severity of skin toxicities when combining these two drugs with irradiation. To our surprise, none of the patients treated showed amifostine-related skin rash or fever, which contrast the results of our previous experience with a similar cohort of patients receiving cisplatin and radiotherapy alone (14). This finding is difficult to explain, but it may suggest an eventual interaction between EGFR skin receptors and immune cells in the pathogenesis of amifostine rash. Repression of the EGFR function in skin by cetuximab may have suppressed the development of amifostine rash.

The incidence of late side effects of RT within a median of 13 months of follow-up was within acceptable levels, despite the hypofractionation applied. Severe laryngeal edema occurred in 9% of laryngeal cancer cases and cervical strictures in 33% of patients with hypopharyngeal carcinoma. Longer follow-up is certainly needed to better estimate late adverse events. It is encouraging that more than half of the nasopharyngeal cancer patients maintained a very good salivary function, in accordance with the established role of amifostine against xerostomia (13).

The efficacy of the regimen was encouraging. The overall complete response rate was 68.5%, and this was as high as 77% in patients who finished therapy without or with minor delays. The 24-month local control rate was 72.3%, while the rate of relapse to distant organs was as low as 6.9%, which may show an effect of cetuximab and cisplatin on micrometastatic disease. These results are similar to the 71% 3-year control rate reported by Pfister *et al.* (23) and are better than the 50% 2-year local relapse-free survival noted in the study by Bonner *et al.* (11). This may show that combined cisplatin and cetuximab therapy may indeed improve the efficacy of RT compared to single-agent radiochemotherapy.

Limitations of our study include a limited follow-up time and a heterogeneous group of patients with locally advanced HNC. However, since the primary endpoint of our study was to evaluate the feasibility of the combination of a highly aggressive, cytoprotection-supported radiochemotherapy regimen that included a targeted agent, the heterogeneity in patient selection is of limited importance. Nevertheless, it is emphasized that longer follow-up is needed to confirm the efficacy results and allow for late toxicities to fully develop. The presence of patients with parotid, skin, and nasopharyngeal cancers, as already discussed, stress that the favorable efficacy reported should be interpreted with caution.

CONCLUSIONS

In conclusion, weekly administration of cisplatin at the dose of 30 mg/m^2 and cetuximab (standard schedule) can be safely combined with accelerated RT, when supported with amifostine cytoprotection. Although the incidence of acneiform rash did not increase with cisplatin, acneiform rash resulted in cetuximab interruption in about one-forth of cases. High daily dose of amifostine (750–1,000 mg) reduces radiation mucositis, allowing completion of therapy with minor delays and, in this study, without the necessity of feeding tubes. The compatibility of cetuximab and amifostine is also documented.

REFERENCES

1. Forastiere AA, Ang KK, Brizel DNY. Head and neck cancers. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, version 2.2008. http://www.nccn.org.
2. Ang KK. Multidisciplinary management of locally advanced SCCHN: Optimizing treatment outcomes. *Oncologist* 2008; 13:899–910.
3. Pignon JP, Bourhis J, Domenge C, *et al*. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. *Lancet* 2000;355:949–955.
4. Bourhis J, Amand C, Pignon J-P, *et al*. Update of MACH-NC (meta-analysis of chemotherapy in head and neck cancer) database focused on concomitant chemoradiotherapy. *J Clin Oncol* 2004;22(Suppl):5505.
5. Bourhis J, Overgaard J, Audry H, *et al*. for the Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. *Lancet* 2006; 368:843–854.
6. Overgaard J, Hansen HS, Specht L, *et al*. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet* 2003;362:933–940.
7. Fu KK, Pajak TF, Trotti A, *et al*. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000;48:7–16.
8. Bourhis J, Lapeyre M, Tortochaux J, *et al*. Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer: A GORTEC trial. *J Clin Oncol* 2006;24:2873–2878.
9. Horiot JC, Le Fur R, N'Guyen T, *et al*. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: Final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiother Oncol* 1992;25:231–241.
10. Brizel DM, Albers ME, Fisher SR, *et al*. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 1998;338: 1798–1804.
11. Bonner JA, Harari PM, Giralt J, *et al*. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567–578.
12. Vermorken JB, Mesia R, Rivera F, *et al*. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116–1127.
13. Brizel DM, Wasserman TH, Henke M, *et al*. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol* 2000;18:3339–3345.

14. Koukourakis MI, Giatromanolaki A, Danielidis V, Sivridis E. Hypoxia inducible factor (HIF1alpha and HIF2alpha) and carbonic anhydrase 9 (CA9) expression and response of head-neck cancer to hypofractionated and accelerated radiotherapy. *Int J Radiat Biol* 2008;84:47–52.
15. Maciejewski B, Majewski S. Dose fractionation and tumour repopulation in radiotherapy for bladder cancer. *Radiother Oncol* 1991;21:163–170.
16. Koukourakis M, Hlouverakis G, Kosma L, *et al*. The impact of overall treatment time on the results of radiotherapy for non-small cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 1996; 34:315–322.
17. Koukourakis MI, Abatzoglou I, Sivridis L, Tsarkatsi M, Delidou H. Individualization of the subcutaneous amifostine dose during hypofractionated/accelerated radiotherapy. *Anticancer Res* 2006;26:2437–2443.
18. Boccia R, Anné PR, Bourhis J, Brizel D, Daly C, Holloway N III, Hymes S, Koukourakis M, Kozloff M, Turner M, Wasserman T. Assessment and management of cutaneous reactions with amifostine administration: Findings of the ethyol (amifostine) cutaneous treatment advisory panel (ECTAP). *Int J Radiat Oncol Biol Phys* 2004;60: 302–309.
19. Eriksen JG, Steiniche T. Overgaard J for the Danish Head and Neck Cancer study group (DAHANCA). The role of epidermal growth factor receptor and E-cadherin for the outcome of reduction in the overall treatment time of radiotherapy of supraglottic larynx squamous cell carcinoma. *Acta Oncol* 2005;44:50–58.
20. Koukourakis MI, Bentzen SM, Giatromanolaki A, *et al*. Endogenous markers of two separate hypoxia response pathways (hypoxia inducible factor 2 alpha and carbonic anhydrase 9) are associated with radiotherapy failure in head and neck cancer patients recruited in the CHART randomized trial. *J Clin Oncol* 2006;24:727–735.
21. Giro C, Berger B, Bölke E, Ciernik IF, *et al*. High rate of severe radiation dermatitis during radiation therapy with concurrent cetuximab in head and neck cancer: Results of a survey in EORTC institutes. *Radiother Oncol* 2009;90:166–171.
22. Pryor DI, Porceddu SV, Burmeister BH, *et al*. Enhanced toxicity with concurrent cetuximab and radiotherapy in head and neck cancer. *Radiother Oncol* 2009;90:166–171.
23. Pfister DG, Su YB, Kraus DH, *et al*. Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: A pilot phase II study of a new combined-modality paradigm. *J Clin Oncol* 2006;24:1072–1078.