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Original article

A randomized phase II study comparing sequential versus simultaneous chemo-radiotherapy in patients with unresectable locally advanced squamous cell cancer of the head and neck

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Summary

Background: Single-modality radiotherapy is still considered standard treatment for patients with locally advanced unresectable cancer of the head and neck. As treatment outcome is poor, attempts to integrate chemotherapy into the overall management of these patients are ongoing.

Patients and methods: A randomized study was undertaken to compare a sequential with a simultaneous chemo-radiotherapy program. Between February 1986 and February 1991, 93 eligible patients with locally advanced unresectable cancer of the head and neck were stratified by WHO PS, T and N class and primary site and then randomized to receive either three courses of neoadjuvant chemotherapy with cisplatin (100 mg/m^2 i.v. d 1) and 5-fluorouracil 1000 mg/m^2/days 1–5 by continuous i.v. infusion every 3 weeks prior to definitive conventional radiotherapy of 65–70 Gy (sequential treatment), or cisplatin 100 mg/m^2 on days 1, 22, 43 given simultaneously for the duration of the same conventional radiotherapy (simultaneous treatment).

Results: At the end of the entire treatment 18 complete responses (47%) in the sequential-treatment arm and 18 (41%) in the simultaneous treatment arm were obtained. No statistically significant differences in the 5-yr progression-free survival, in the median time to loco-regional and distant progression and in the 5-yr overall survival were observed. Leukopenia was more frequent in the simultaneous than in the sequential arm ($p = 0.03$), whereas alopecia ($p = 0.008$) and phlebitis ($p < 0.0001$) were more frequent in the sequential-treatment arm. A better compliance was associated with the concomitant treatment, with 87% of the patients completing the entire radiotherapy program versus 63% of those in the sequential arm ($p = 0.01$).

Conclusions: In the present study, the two treatment arms showed similar activity (complete response, progression-free and overall survival rates). Compliance to treatment was better in the concomitant arm. These data suggest that concomitant chemo-radiation therapy might be considered an option in unresectable locally advanced cancer of the head and neck. Phase III studies are needed in order to establish the superiority of this combination of cisplatin and radiotherapy versus radiotherapy alone.

Key words: chemo-radiotherapy, head and neck squamous cell cancer

Introduction

Prognosis for patients with cancer of the head and neck region depends upon the site of origin, the local and regional extent of tumor and the patients' Karnofsky status. Cure rates for early-stage tumors are generally extremely high. More advanced tumors are more complicated and more difficult to manage.

In a RTOG series of inoperable patients treated with radiation alone, the median survival was 13.3 months and the overall five-year survival was 18% [1].

Several clinical studies have demonstrated the responsiveness of squamous cell head and neck cancer to both single-agent and combination chemotherapy, particularly in previously untreated patients. Nonetheless, attempts to integrate combination chemotherapy into the overall management of patients with locally advanced head and neck cancer have yielded controversial results.

Neoadjuvant chemotherapy has proven able to induce major tumor shrinkage but no true survival benefits have been observed in randomized trials [2–8].

In terms of local control and progression-free survival, some phase III randomized trials have demonstrated the superiority of treatment schedules using simultaneous chemo- and radiotherapy over those employing radiation therapy alone [9–13]. However, the differences involved fairly small percentages and a higher long-term overall survival was demonstrated in only two studies [11, 12]. Other randomized studies reported completely negative results [14–16]. For these reasons some of these concomitant programs have not yet been adopted as standard treatment.

More recently, pilot studies have used split-course radiotherapy schedules with intensified concomitant chemotherapy [17–19]. While local control and survival data of several of these studies are impressive, acute toxicity is substantial (particularly excessive mucosal

reactions). However, they still require confirmation in larger randomized studies to accurately assess their impact on local and distant control rates and chronic toxicity.

A RTOG phase II study of concomitant cisplatin and radiation in locally advanced and inoperable tumors of the head and neck showed a very encouraging 70% complete response rate [20]. Patient compliance with this treatment was also acceptable.

To test this regimen still further, we decided to compare it with a sequential chemo-radiotherapy program in a randomized phase II trial in order to select the best regimen for subsequent testing against standard therapy (radiotherapy alone). The chemotherapy regimen chosen for the sequential arm was the cisplatin – 5-fluorouracil combination. This employs three cycles of induction chemotherapy with cisplatin and a five-day continuous infusion of fluorouracil. This combination, given prior to local therapy, has been extensively studied. Overall response rates have ranged from 38% to 100% and CR rates from 13% to 54% [7, 21].

Patients and methods

The study was conducted in 97 patients treated at the Regina Elena Cancer Institute of Rome between February 1986 and February 1991. All patients had histologically documented, measurable, locally advanced (stage III and IV) inoperable squamous cell carcinoma of the head and neck region and no prior treatment. A complete blood count, urinalysis, electrocardiogram and serum chemistry tests including urea nitrogen, creatinine, calcium, phosphorus, alkaline phosphatase, serum glutamic oxaloacetic and piruvic transaminases, albumin, total protein, bilirubin and uric acid were performed on all of the patients. To evaluate possible distant spread of the disease in addition to performing a thorough physical examination, all patients were studied with pretreatment chest X-ray, cat scan, liver echography and bone scintigraphy. All underwent a pretreatment dental evaluation and received appropriate treatment.

All of the patients were under 76 years of age with a World Health Organization (WHO) performance status (PS) of 0 to 2, adequate renal function, as demonstrated by serum creatinine <1.5 mg/dL and creatinine clearance >60 ml/min, adequate hepatic function (bilirubin <15 mg/dL), leukocyte count >4,000/dL, platelet count >100,000/dL.

Informed consent was required for study entry. The clinical research review board of the Regina Elena Institute approved the study.

At the time of enrollment, the patients were evaluated by a surgeon, a radiotherapist and a medical oncologist. The disease stage was established according to the 1983 American Joint Committee System [22].

After giving informed consent, the patients were stratified according to PS (0–1,2) primary site, (oral cavity, oropharynx, other) T(T1–3, T4) and N(N0–1, N2, N3) classifications and then randomized to receive either the sequential or the simultaneous treatment.

The sequential treatment consisted of three courses of the cisplatin–5-fluorouracil chemotherapy regimen (cisplatin, 100 mg/m^2 i.v. on day 1, and 5-fluorouracil 1,000 mg/m^2/d as a continuous i.v. infusion for 120 hours). Cisplatin was administered together with hydration and forced diuresis in both regimens. Patients with a complete response or disease progression after two courses of chemotherapy did not receive the third course.

Subsequent radiotherapy given with a 10 MV linear accelerator was initiated 10–20 days after the last chemotherapy dose. The tumor dose was 65 to 70 Gy, delivered by two lateral, symmetrical opposing fields including the primary lesion and regional lymph nodes. Five fractions per week of 2 Gy each were employed with both sides irradiated daily.

The simultaneous treatment consisted of three courses of chemotherapy with cisplatin (100 mg/m^2 i.v.), given in the same modalities as the other arm, administered every 3 weeks beginning on day 1 of radiotherapy for a total of three courses. The same radiotherapy as in the sequential arm was used.

The response evaluation was performed by the otolaryngologist and by both the radiation and medical oncologist at the end of the chemotherapy program and again two months after the end of radiotherapy in the sequential-treatment arm; in the concomitant treatment arm the response evaluation was done two months after the end of the combined chemo-radiotherapy program.

Complete response (CR) was defined as the disappearance of all clinically evident disease. Partial response (PR) was defined as a more than 50% decrease in the sum of the products of the largest perpendicular diameters of the measurable lesions lasting for at least 4 weeks. Stable disease (SD) was considered an objective response without satisfying the PR criteria, with an increase of less than 25% or no change in the disease status. Progressive disease (PD) was considered a more than 25% increase of these measurements or the appearance of new lesions.

To define an objective response, a minimum of two courses of chemotherapy were required, unless a clear disease progression occurred during treatment.

Patients who had a major toxicity or died of the treatment were considered progressive. Performance status and toxicity criteria were those adopted by the WHO. During the follow-up blood tests and physical examinations were performed every two months and a chest X-ray every four months during the first two years; thereafter, the patients were examined every 4–6 months. Weekly i.v. methotrexate at a dose of 40 mg/mq was the second-line chemotherapy adopted in the majority of the patients. No patient was submitted to surgery for either residual or recurrent disease.

Progression-free and overall survival were dated from the on-study day to the date of tumor progression or death, respectively.

Statistical methods

The study was planned to include 50 patients in each arm. This sample size permitted estimation of the CR rate with a standard error of about 7%.

The CR rate was the principal end point of this randomized phase II study; other end points were progression-free survival, toxicity and also the feasibility of the treatment, particularly of the chemo-radiation concomitant arm.

Patient characteristics, response rates and toxicity of the two treatment arms were compared by means of the chi-square test. Survival curves were calculated according to the Kaplan-Meier [23] method and the differences between them were evaluated by the log-rank test [24].

Results

Ninety-seven patients entered the study between February 1986 and February 1991.

Four patients (4%) were considered ineligible, based on the blinded review of eligibility criteria and were therefore excluded from all the analyses. Three of the ineligible patients had been randomized in the sequential treatment arm and one in the simultaneous arm. Reasons for exclusion were: incorrect histology, WHO PS of 3, operable disease and unknown primary site.

Of the 93 eligible patients, 82 were male and 11

female. The median age was 57 years (range 20–75 years); median WHO PS was 1 (range 0–2). The site of the primary tumor was the oral cavity in 45%, the oropharynx in 24%, the hypopharynx in 11%, the nasopharynx in 11% (all squamous cell cancers), the larynx in 8% and the maxillary sinus in 1% of the patients. Eighty-three percent of the patients had stage IV and 17% had stage III disease; 57% of the patients presented T4 and 32% N3 lesions. Patients were evenly distributed in the treatment groups according to tumor site, disease stage, T and N class. The groups were also comparable with regard to a variety of other potential prognostic factors including WHO PS, age and sex (Tables 1, 2).

All of the patients were evaluable for toxicity, but 11 patients were not evaluable for response to the combined treatments because of major protocol violations (sequential: 2, simultaneous: 5), refusal (sequential: 3), lost to follow-up (sequential: 1).

Responses

Of the 44 patients evaluable for response to the induction cisplatin-fluorouracil chemotherapy (including 2 early deaths due to toxicity) 12 (27%) achieved a CR and 13 (30%) achieved a PR for an overall response rate of 57%. Seventeen patients, 13 showing no change and 4 disease progression, did not respond to the treatment.

Table 1. Patient characteristics.

	Sequential	Simultaneous
No. of patients	44	49
Median age (range)	58 (38–73)	57 (20–75)
Sex: M/F	43/1	39/10
WHO PS		
0–1	34	40
2	10	9
Stage		
III	6	10
IV	38	39
Primary site		
Oral cavity	21	21
Oropharynx	9	13
Hypopharynx	4	6
Nasopharynx	3	7
Larynx	7	1
Maxillary sinus	/	1

Table 2. Tumor and node stages of the treatment groups.

	Sequential				Simultaneous			
	T2	T3	T4	All	T2	T3	T4	All
N0	0	3	12	15	0	7	8	15
N1	1	3	5	9	0	3	8	11
N2	0	6	1	7	0	3	4	7
N3	3	2	8	13	4	3	9	16
All	4	14	26	44	4	16	29	49

At the end of the entire treatment, 18 CRs (47%, confidence interval 30%–62%) and 5 PRs (13%) in the sequential treatment arm and 18 CRs (41%, confidence interval 27%–55%) and 15 PRs (34%) in the simultaneous treatment arm were observed (Table 3). With regard to CR and overall response the differences between arms A and B were not statistically significant (p = NS).

Table 3. Response to combined treatments.

	Sequential (38 pts)		Simultaneous (44 pts)	
	No. of pts	%	No. of pts	%
CR	18	47.4 (95% confidence limits: +/− 15.9)	18	40.9 (95% confidence limits: +/− 19.9)
PR	5	13.2	15	34.1
SD	3	7.9	4	9.1
PD	10	26.3	7	15.9
Early death (toxicity)	2	5.2	/	/

p = NS.

Toxicity

Table 4 shows the incidence of the most severe hematologic and non-hematologic toxicity. Twenty-eight patients (64%) in the sequential and 41 patients (84%) in the simultaneous arm experienced leukopenia (Grade 3–4: 9% versus 25%); this difference was statistically significant at a P value of 0.03. However no patient had a grade 4 leukopenia and only one patient (simultaneous arm) had a neutropenic fever. By contrast, there were no statistically significant differences in the two treatment arms with regard to thrombocytopenia and anemia.

As far as non-hematologic toxicity is concerned,

Table 4. Toxicity according to WHO criteria.

	Sequential (44 pts)		Simultaneous (49 pts)		p
	GR 1-2	GR 3-4	GR 1-2	GR 3-4	
Leukopenia	24	4	29	12	0.03
Platelets	17	3	11	1	N.S.
Anemia	20	1	13	5	N.S.
Emesis	16	9	20	14	N.S.
Mucositis	22	13	29	12	N.S.
Diarrhea	12	/	7	/	N.S.
Alopecia	14	3	5	/	0.008
Renal	19	/	15	1	N.S.
Neuropathy	1	/	2	/	N.S.
Cardiac	/	1	/	/	N.S.
Phlebitis	14	5	/	/	<0.0001
Weight loss >10%	2		7		NS

Toxicity GR 5: Sequential: 2 pts (renal; diarrhea).
Simultaneous: 1 pt (renal).

alopecia (39% versus 10%) and peripheral phlebitis (43% versus O) were more frequent in the sequential-treatment arm due to the 5-fluorouracil administration. Seven patients in the sequential-treatment arm and two patients in the simultaneous-treatment arm had a weight loss >10% at the end of the entire treatment program (p = NS). No significant differences for the other side effects were observed. Overall only 12 patients (7 sequential, 5 simultaneous arm) experienced a WHO grade 4 toxicity: emesis (6 patients) mucositis (3 patients), peripheral phlebitis (1 patient), anemia (1 patient), thrombocytopenia (1 patient). Three patients (2 sequential: renal, 1 simultaneous arm: febrile neutropenia) died of toxic effects.

Patient compliance with the treatments is summarized in Table 5. Eighty-seven percent of the patients in the simultaneous-treatment arm completed the radiotherapy versus 63% in the sequential arm. This difference was statistically significant at a P value of 0.01. Sixty-seven percent of the patients completed both the radio- (65–70 Gy) and the chemotherapy (three courses) in the simultaneous treatment arm versus 57% in the sequential arm; this difference was not significant. Patient refusal, prohibitive toxicity and disease progression were the principal reasons for not completing the treatment plan.

The prohibitive toxicities were represented by renal toxicity in three patients (two early deaths), persistent leukopenia in one patient and myocardial ischemia in one patient in the sequential arm; and severe leukopenia in 4 patients (1 early death), renal in two patients, severe mucositis in one patient, anemia and poor general conditions in one patient.

Disease recurrences

Of the patients with complete responses, local or regional relapses occurred in 12 of the 18 patients (67%) in the sequential treatment (in 8 patients at the T level, in 2 patients at the N level and in another 2 patients at both the T and N levels) and in 7 of the 18 patients (39%) in the concomitant treatment (in 4 patients at the T level and in 1 patient at the N level and in 2 patients at both the T and N levels). The difference was not statistically significant.

Distant metastases were observed in 7 patients in the sequential arm and in 4 in the concomitant arm (16% vs. 8%, P = NS). Sites of metastases were: lungs (6 patients), liver (2 patients), bone (1 patient), epidural space resulting in spinal cord compression (1 patient) and bone and lungs (1 patient).

Second primaries were observed in 4 patients, 2 in each group. Two were tumours of the oropharynx and 2 of the lung (squamous cell).

Table 5. Treatment compliance.

	Sequential (44 pts)		Simultaneous (49 pts)		p
	No. of pts.	%	No. of pts.	%	
RT delivery finished RT (70 Gy)	28	63	43	87	0.01
CT delivery received 3 courses	37	84	37	76	NS
Received 1–2 courses	7	16	12	24	
Combined modality RT (70 Gy) + CT (3 courses)	25	57	33	67	NS
Not completed	19	43	16	33	
Patient refusal	5		3		
Prohibitive toxicity	5		8		
Disease progression	1		2		
Other			3		

Survival

Figure 1 shows the progression-free survival curves computed by means of the Kaplan-Meier method. At 5 years, progression-free survival was 16% for the sequential and 20% for the simultaneous treatment. The median progression-free survival was 9 months for the former and 10 months for the latter group, showing no statistically significant differences.

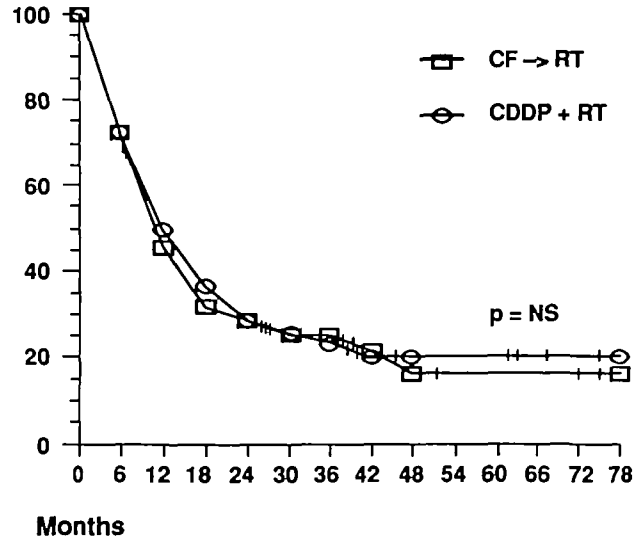

Fig. 1. Progression-free survival. Tickmarks represent patients alive and without sign of disease progression.

The time to loco-regional progression was the same in the two treatment groups (median 11 months in both) as shown in Fig. 2. No statistically significant differences were found with regard to time to appearance of distant metastases (Fig. 3).

Figure 4 shows the overall survival curves computed with the Kaplan-Meier method. At 5 years, the overall survival rate was 11% for the sequential treatment and 16% for the simultaneous treatment. The median survival was 10 and 18 months, respectively, showing no statistically significant differences (P = 0.27).

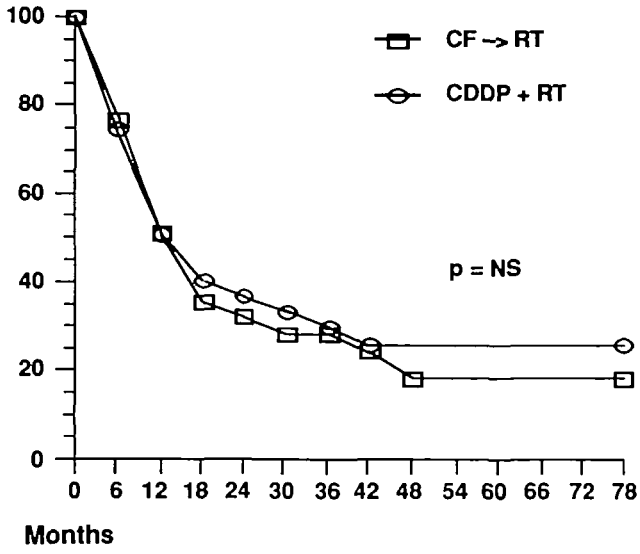

Fig. 2. Time to loco-regional progression.

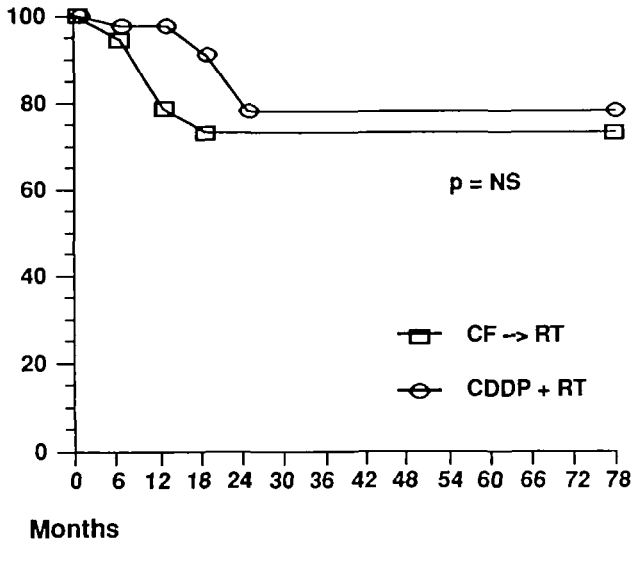

Fig. 3. Time to distant metastases.

Discussion

The present study was planned to include only patients with poor-prognosis inoperable locally advanced head and neck cancers (stage III and IV). This study is actually a comparison of two experimental arms without a control population. The combination of cisplatin and radiotherapy was the same as that used in a phase II study conducted by the RTOG [20], which proved to be effective and safe for patients with advanced inoperable head and neck cancer. Therefore, this randomized phase II study was activated in order to select the best regimen for a subsequent trial testing it against standard therapy (radiotherapy alone).

The complete response rate was the principal end point of this randomized phase II study; other end points included comparison of toxicity and progression-free survival between the two arms.

The two treatment arms showed similar activity. In

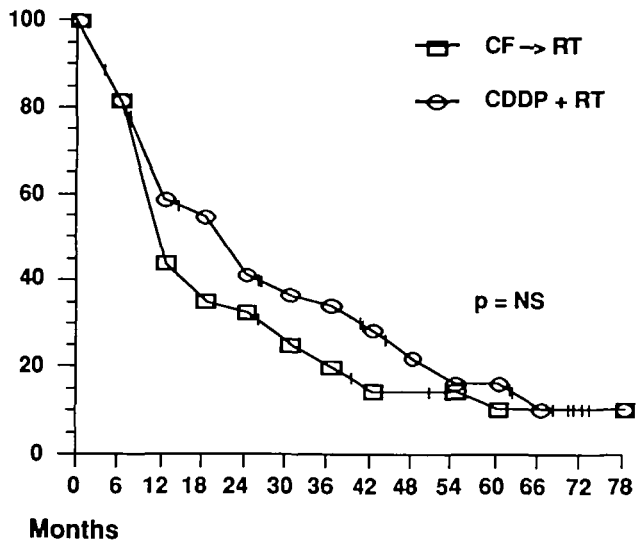

Fig. 4. Overall survival. Tickmarks represent patients alive.

fact, both the complete response and survival rates (progression-free and overall) were similar. The complete response rates obtained in both arms seem to be higher than those reported for radiotherapy alone in the same subset of patients [1, 11]. The incidence of both loco-regional and distant metastases in the patients with complete response after combined treatments was lower in the concomitant-treatment arm than in the sequential one; however, no significant differences in the time to loco-regional or distant progression were observed.

The simultaneous treatment was also slightly better tolerated. In fact, patient refusal, because of prohibitive toxicities, were more frequent in the sequential-treatment arm. The incidence of severe leukopenia was significantly higher in the simultaneous arm but only one patient had a neutropenic fever. A weight loss greater than 10% was more frequently observed in the patients submitted to the simultaneous arm, but the difference was not statistically significant. Both the incidence and the intensity of mucositis were the same in the two treatment groups, thus confirming that this side effect increases greatly when drugs such as bleomycin, methotrexate or 5-fluorouracil are given concurrently with radiotherapy. In fact the simultaneous delivery of these drugs with radiation often required interruption of the treatment in order to avert such severe reactions. Our results confirm that these severe toxic effects common to concomitant chemo-radiotherapy may be avoided by carefully choosing drugs that have no cross-toxicity with radiotherapy.

Single-modality radiotherapy is today considered standard treatment for patients with locally advanced inoperable head and neck cancer. However, response rates are limited and survival rates are very low [1]. In addition, the treatment outcome is poor and unsatisfactory as standard therapy.

In order to improve survival rates a series of randomized trials of induction chemotherapy followed by

definitive loco-regional treatment have been conducted in the past 10–15 years. High response rates were obtained in virtually all of the studies that included combination chemotherapy prior to local treatment, as induction or neoadjuvant therapy [25–30]. In our previous report [30], a complete response to neoadjuvant chemotherapy was found to be the most powerful predictor of long-term survival. However, chemotherapy preceding radical radiotherapy failed to consistently influence the long-term results in controlled studies [6–8]. Limitations in the design and conduct of most of these studies have, however, been observed, including the use of ineffective chemotherapy regimens, a limited number of cycles, a poor stratification method, poor patient compliance for locoregional treatment after induction chemotherapy and inadequate statistical power.

The integration of chemotherapy with radiotherapy in the treatment of patients with head and neck cancers continues to be an area of active clinical effort. Mature details from randomized trials were reported [9, 10, 12, 13], and thereafter, phase II studies with intensive concurrent combination chemotherapy and radiotherapy programs showed very high response rates and, more importantly, confirmed the durability of the responses [17–19]. Treatment-related side effects have most commonly included severe weight loss, mucositis and moderate-to-severe myelotoxicity due to the overlapping toxicity of some cytotoxic drugs used in head and neck cancer and radiation therapy.

During the past two decades, other trials have compared radiotherapy alone with single-agent chemotherapy combined with radiotherapy. It should be noted that most of these trials used suboptimal chemotherapy, probably because their main goal was to exploit the radiosensitizing effect of the cytotoxic drugs. The strategy of our study is completely different: its objective is to search for an additive or synergistic effect resulting from the simultaneous combination of two active treatments.

Finally it should be stressed that in the concomitant treatment the overall survival figures were exactly the same as those obtained by the RTOG some years ago in patients with disease at the same stage, treated with radiation therapy alone. In this regard, however, we should consider the small patient population of this study and the fact that analysis of overall survival was not among the objectives of the study.

Notwithstanding the limited number of patients in this study, some important conclusions can be drawn. Neoadjuvant chemotherapy prior to radiation treatment should not be considered an option for the treatment of patients with locally advanced inoperable disease. In fact, the long duration of the entire program and the related side effects often compel the patients to delay or interrupt treatment. In addition, no survival benefits in phase III studies were found in a comparison of the sequential approach to radiotherapy alone.

The improved treatment outcome reported in some studies in patients treated with concomitant chemo-radiotherapy suggests that this line of research should be rigorously pursued. There is clear evidence that the efficacy of such regimens is greater when more intensive chemotherapy-radiotherapy programs, which also induce a great increase of both the incidence and intensity of treatment-related side effects, are adopted. Future studies to investigate a more satisfactory balance between the treatment activity and toxicity of these regimens are warranted. For the above-mentioned reasons, treatment of patients in clinical studies should be given high priority, and rather than pursue historical single-modality approaches, medical oncologists and radiation oncologists should work closely together to better define optimal schedules of combined treatments for inoperable locally advanced head and neck cancer patients. For patients who are not eligible to enter clinical trials, the data published thus far suggest that concomitant chemo-radiation therapy might be a reasonable option, even though its toxic effects, patient characteristics and preexisting medical problems in most cases constitute a real obstacle to carrying out these programs. Lastly, concomitant chemo-radiotherapy should be considered for phase III trials comparing this adjuvant approach to the more conventional post-surgical radiotherapy in high-risk locally advanced surgically-treated patients in an attempt to reduce the risk of both local recurrence and distant metastases.

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