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ORIGINAL ARTICLE

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Neo-adjuvant chemo-(immuno-)therapy of advanced squamous-cell head and neck carcinoma: a multicenter, phase III, randomized study comparing cisplatin + 5-fluorouracil (5-FU) with cisplatin + 5-FU + recombinant interleukin 2

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Abstract We carried out an open, randomized, phase III, multicenter clinical trial to compare, in neo-adjuvant setting, the clinical response and toxicity of the combination chemotherapy cisplatin + 5-FU with the same combination plus s.c. recombinant interleukin-2 (rIL-2) in patients with advanced (stage III–IV) head and neck squamous-cell carcinoma (HNSCC). Regimen A was the classical Al Sarraf treatment: 100 mg/m^2 cisplatin i.v. on day 1 plus 1000 mg m^{-2} day^{-1} 5-FU on days 1–5 as a continuous infusion. Regimen B was the same as regimen A plus 4.5 MIU/day rIL-2 s.c. on days 8–12 and 15–19. Treatment was repeated every 3 weeks for three cycles. A total of 33 patients were enrolled in the study; 30 were evaluable for toxicity and 28 for response. Seventeen patients were assigned to group A and 16 were assigned to group B. Three patients (20%) of group A and 4 (31%) of group B had a complete response, 9 patients (60%) of group A and 6 (46%) of group B had a partial response, with an overall response rate of 12 patients (80%) for group A and 10 patients (77%) for group B. Two patients (13%) of group A and 3 patients (23%) group B had stable disease; 1 patient (7%) of group A had progressive disease. Thus, there was not a statistically significant difference in response rate between the two groups and therefore there was no benefit from the addition of immunotherapy with rIL-2 to the standard chemotherapy. Both regimens were well tolerated. There were 2 toxic deaths (6.7%), 1 from hematological causes in group A and 1 from cardiac causes in group B. Myelosuppression and gastrointestinal toxicity, mainly nausea/vomiting and stomatitis, were the most frequent toxicities. The calculated number of patients for the sample has not yet been reached; however, the projection of our present results suggests that it is highly improbable that a clinically significant difference between the two treatment groups will be observed even if the calculated patient sample size is achieved.

Key words Cisplatin · rIL-2 immunotherapy · Neo-adjuvant chemotherapy · Randomized phase III trial · Squamous-cell head and neck carcinoma

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Introduction

The purpose of neo-adjuvant chemotherapy (NAC) for head and neck squamous-cell cancer (HNSCC) is to improve the ability of this strategy, followed by loco-regional standard treatments, to eradicate micro-metastatic lesions and, as demonstrated more recently, to achieve organ preservation without compromising overall survival [27].

In 11 studies comprising a total of 346 patients the combination of cisplatin and 5-fluorouracil (5-FU),

which is the most active and most extensively used regimen in a neo-adjuvant setting, yielded an overall response rate (ORR) of 66%–77% (range 56%–100%) with a complete response (CR) rate of 20%–35% (range 13%–66%) [3]. The addition of vinorelbine to cisplatin + 5-FU did not add a significant advantage, yielding an ORR of 88% with a CR rate of 23% in 60 patients [10], and similar results were obtained with a combination of ifosfamide (2.2 g m^{-2} day^{-1}) and cisplatin (10 mg m^{-2} day^{-1}) on days 1–5 [21].

In HNSCC, six conclusive randomized trials have compared NAC with cisplatin and 5-FU followed by loco-regional treatment with loco-regional treatment alone [6, 12, 15, 16, 20]. The most important results of these studies can be briefly summarized: (1) the patients with CR to chemotherapy had a longer survival than non-responders irrespective of any subsequent treatment, (2) the patients with negative histology after NAC had a better survival than those with microscopic disease in the surgical specimen, (3) NAC did not increase the morbidity following surgical resection, (4) NAC administration decreased the incidence of distant metastases as the site of first failure and, most significantly, (5) the single studies utilizing NAC generally failed to show a significant survival benefit, since failure to maintain local control is the main cause of death in HNSCC [32].

Although thus far the degree of improvement in survival following adjunctive chemotherapy has been modest [11], this trend has emerged in recent reviews [7, 36] and its statistical validity confirmed in a recent meta-analysis [8] showing that the addition of chemotherapy to local treatment has reduced the mortality rate for treated patients by 11% in all 25 studies examined.

The suggested new directions of NAC involve biochemical modulation of 5-FU with 1-leucovorin [34] and the incorporation of interferon α (IFNα) as a second modulator [35], whereas, at the present time, there is little information about the clinical activity of paclitaxel and docetaxel in this setting.

Theoretically, a combination of biological agents and cytotoxic agents should be synergistic for treating cancer, because the agents have different mechanisms of action.

Since HNSCC in its natural history tends to local recurrence, local immunotherapy could be considered a rational approach. In a pilot study, Cortesina obtained an ORR of approximately 20% in 20 recurrences of HNSCC with local intralymphatic injection of low doses of recombinant interleukin 2 (rIL-2) [5] but local rIL-2 administration is no longer used. The combination of intravenous (i.v.) rIL-2 and intramuscular (i.m.) IFNα produced a favourable clinical response though relevant toxic effects were observed [23, 28]. The combination of cisplatin, 5-FU and i.v. rIL-2 was found tolerable and active in phase II studies [30], as well as the combination of carboplatin, 5-FU, rIL-2 and IFNα [24]. In a phase II study, one of us [1] obtained good clinical results with an ORR of 53% and acceptable toxic effects using subcutaneous (s.c.) rIL-2 at a dose of 4.5 MIU daily on days 8–12 and 15–19 every 21 days in combination with cisplatin + 5-FU in recurrent disease.

In a previous non-randomized phase II study we compared, in neo-adjuvant setting, the combination cisplatin, 5-FU and vinorelbine with the same combination plus s.c. rIL-2 at a dose of 9 MIU daily from day 9 to 13 and from day 16 to 20 for every cycle in 21 patients with advanced HNSCC [17]. Though the number of patients was very small, the ORR was particularly high (100%) in the arm containing rIL-2. We concluded that such a combination was highly active though rather toxic.

Those results prompted us to carry out an open, randomized phase III, multicenter trial to compare, in neo-adjuvant setting, the clinical response and toxicity of the combination chemotherapy cisplatin + 5-FU with the same combination plus s.c. rIL-2 in patients with advanced (stage III–IV) HNSCC. We decided to use a less toxic regimen than that previously used and we tried to achieve this goal by reducing the number of drugs in the combination and the dose of rIL-2. Consequently, we decided to remove vinorelbine which, though effective as a single agent [9], did not seem to add a substantial advantage when combined with cisplatin and 5-FU even in our previous study [10], and to reduce by half the dose of rIL-2 to minimize its characteristic toxic effects.

Patients and methods

Patient population

From August 1995 to August 1996 33 patients (M/F: 29/4, mean age 54.5 years, range 38–72 years), hospitalized in the participating centers[1] were enrolled in the study. The randomization was centralized in the Division of Medical Oncology, S. Giovanni Hospital, Turin.

Patients' entry criteria included the following:

1. Histologically confirmed technically resectable or unresectable stage III–IV HNSCC, according to the staging system of the UICC [13] and AJCC [2]
2. Measurable disease
3. No previous treatment for the actual disease
4. ECOG performance status 0–1 and a life expectancy of at least 6 months
5. Age 18–75 years
6. White blood cell count more than 4000/μl, platelet count more than 100 000/μl, serum bilirubin less than 2 mg/dl, creatinine clearance more than 60 ml/min
7. Informed consent
8. At least a 4-week interval from whatever surgery and 2 weeks from the taking of biopsy specimen
9. Absence of any infection requiring antibiotic treatment
10. Adequate nutritional and liquid supply.

Patients' exclusion criteria included the following:

1. Prior treatment excluding diagnostic biopsy
2. Distant metastases
3. A history or the presence of a second malignancy except for basal cell carcinoma of the skin and cervical carcinoma in situ

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4. Serious hearing impairment
5. Clinical evidence of congestive heart failure grade III–IV (New York Heart Classification)
6. Drug-uncontrolled angina pectoris
7. Drug-uncontrolled clinically significant cardiac arrhythmia
8. Drug or chronic alcohol addiction
9. Women of childbearing age without a negative pregnancy test
10. Previous or presently hypercalcemia.

All patients were initially evaluated by an otolaryngologist and a medical oncologist. The initial evaluation included a medical history, clinical examination, upper aerodigestive tract endoscopy, chest X-ray, upper-abdomen echography, bone scintigraphy, complete blood cell count, complete blood chemistry, urinanalysis and an electrocardiogram. When indicated, computerized tomographic (CT) scans of the chest, abdomen, and head and neck regions were obtained. At the end of the study an identical evaluation was performed. Written informed consent was obtained from each patient prior to treatment, according to the guidelines of the Ethics Committee of the Department of Internal Medicine, University of Cagliari.

Treatment plan

Eligible patients were randomly assigned to receive one of two different induction chemotherapy regimens. Regimen A was the classical Al Sarraf treatment: 100 mg/m^2 cisplatin i.v. as a 60-min infusion on day 1, with a standard pre- and post-hydration protocol with forced diuresis by 250 ml 18% mannitol, plus 1000 mg m^{-2} day^{-1} 5-FU on days 1–5 (120 h) as a continuous infusion (c.i.) by peripheral vein. Regimen B was the same as regimen A plus 4.5 MIU/day rIL-2 (Proleukin, Chiron, Milan, Italy) s.c. on days 8–12 and 15–19, repeated every 3 weeks for three cycles. Three treatment cycles were planned for regimens A and B unless the patient experienced progressive disease (PD) or unacceptable toxicity. At the end of the third cycle the patients were evaluated for response and subsequently the most adequate loco-regional treatment, either surgery or radiation therapy or both, was given. In some cases where previously inoperable patients achieved a high-grade partial response (PR), a further two or three cycles were administered but their further response is not reported in this study. Patients in PD were offered either loco-regional treatment or chemotherapy. Antiemetic therapy with i.v. 5-hydroxytryptamine receptor type 3 antagonists ($5HT_3RA$) plus dexamethasone on day 1 and oral $5HT_3RA$ on days 2–5 plus antipyretics was administered to all patients to control side-effects of treatment.

If the patients developed World Health Organization grade II [38] stomatitis, the dose of 5-FU was reduced by 25% in the subsequent cycle; if grade III stomatitis occurred, it was reduced by 50%; if grade IV stomatitis occurred, chemotherapy was stopped. The dose of cisplatin was reduced by 50% if there was a transient elevation in the serum creatinine levels taking them to 2.5–5 times the normal upper limit; if the renal function did not revert to normal by the first day of the next cycle, cisplatin treatment was withheld. If the patient had a white blood cell count below 4000/μl or a platelet count below 100 000/μl, the treatment was delayed until the count normalized within a maximum of 4 weeks. Hematopoietic growth factors (granulocyte- or granulocyte/macrophage-colony-stimulating factor: G-CSF or GM-CSF) were administered at the appearance of leukopenia/neutropenia that could potentially delay the chemotherapy administration (nadir granulocyte count below 500 μl). Treatment was interrupted if grade III toxicity other than hematological, oral or renal toxicity, occurred. rIL-2 treatment was interrupted if grade IV toxicity of any organ system occurred, the dose was reduced by 50% in the case of grade III toxicity; if the toxicity persisted, rIL-2 was completely withdrawn.

Evaluation of response and toxicity

Patients were evaluable for response to treatment if they received three cycles of therapy. Objective tumor regression, as well as toxicity, were evaluated according to WHO criteria [18]. Briefly, a CR was defined as the disappearance of all signs of disease for at least 4 weeks, i.e. a normal clinical examination with the absence of tumor and/or cervical nodes, a normal endoscopy and CT scan showing no evidence of tumor, and negative biopsies on the primary tumor size; a PR was defined as more than 50% reduction in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 4 weeks without the appearance of any new lesion; stable disease (SD) as less than 50% decrease or less than 25% increase in the size of tumor deposits; and PD as more than 25% increase in the size of tumoral lesions or the appearance of any new lesion.

The dose intensity of the chemotherapy delivered was calculated for all patients who were evaluable for response. The total quantity (m^{-2}) of each drug delivered to all patients evaluable for response was divided by the total duration of treatment of all evaluable patients.

Toxicity was assessed according to WHO criteria [18].

Statistics

The sample size necessary to demonstrate a 20% difference between the two regimens at the significance level of $\alpha = 0.05$ with a power of $\beta = 0.80$, was calculated to be 95 patients per arm.

An interim analysis, carried out on the first 30 patients, is presented in this study.

Statistical evaluation

The Yates-corrected χ^2-test was performed.

Results

Patients

A total of 33 patients were enrolled in the study, 3 patients were not evaluable because they refused treatment; 30 patients (M/F 27/3, mean age 56 years, range 39–72 years) were evaluable for toxicity and 28 patients (M/F 26/2, mean age 56 years, range 39–72 years) were evaluable for response.

Seventeen patients were assigned to group A and 16 were assigned to group B; the patient clinical characteristics are shown in Table 1. The two groups were well balanced for sex, age, site of primary tumor, tumor grade, ECOG performance status and clinical stage. One patient of group A died from hematological toxicity (febrile neutropenia grade IV associated with infection) having received only one cycle and one patient of group B died from cardiac toxicity having received two cycles: both were considered not evaluable for antitumor response as they died too early.

Response to treatment

Out of 17 patients assigned to group A, 16 received NAC as planned; the remaining patient refused treatment. Out of 16 patients assigned to group B, 14 received NAC as planned: the remaining 2 patients refused treatment. All but 2 patients who died for treatment toxicity received three cycles.

Table 1 Patient clinical characteristics

Characteristic	Group A	Group B
Enrolled	17	16
Sex		
Male	15	14
Female	2	2
Mean age and range (years)	54.41 (38–72)	56.75 (48–66)
Evaluable for toxicity	16	14
Sex		
Male	15	12
Female	1	2
Mean age and range (years)	55.44 (39–72)	56.57 (48–66)
Evaluable for response	15	13
Sex		
Male	14	12
Female	1	1
Mean age and range (years)	56.00 (39–72)	55.85 (48–63)
Site of primary tumor		
Hypopharynx	2 (11.76%)	2 (12.50%)
Larynx	3 (17.75%)	5 (31.25%)
Oropharynx	9 (52.94%)	6 (37.50%)
Oral cavity	2 (11.76%)	2 (12.50%)
Rhinopharynx	1 (5.88%)	–
Undefined	–	1 (6.25%)
Tumor grade (degree of squamous differentiation)		
Well differentiated G1	2 (11.76%)	1 (6.25%)
Moderately differentiated G2	7 (41.18%)	10 (62.50%)
Poorly differentiated G3	8 (47.06%)	5 (31.25%)
ECOG performance status		
0	10 (58.82%)	12 (75%)
1	7 (41.18%)	4 (25%)
Clinical stage		
Stage III		
T3 N0	1	2
Total	1 (5.88%)	2 (12.50%)
Stage IV		
T0 N3	–	1
T2 N2	–	1
T3 N2	2	2
T3 N3	–	1
T4 N0	1	2
T4 N1	6	3
T4 N2	7	4
Total	16 (94.12%)	14 (87.50%)

Table 2 Clinical response of the two groups. *5-FU* 5-fluorouracil, *IL-2* interleukin-2

Response	Group A:cisplatin + 5-FU		Group B: cisplatin + 5-FU + IL-2			
	No. patients	(%)	No. patients	(%)	$\chi^{2\,a}$	*P*
Overall response	12	80	10	77	0.07	0.79
Complete response	3	20	4	31	0.05	0.83
Partial response	9	60	6	46	0.12	0.72
Stable disease	2	13	3	23	0.00	1.00
Progressive disease	1	7	–	–	0.01	0.94
Total	15		13			

[a] Yates-corrected χ^2-test

Three patients (20%) of group A and 4 patients (31%) of group B had CR. The ORR of group A was 80% and that of group B was 77% (Table 2). It is worth noting that the majority (60%) of patients who had PR achieved a high-grade response, i.e. at least 75%. Thus, there was no statistically significant difference in response rate between the two groups and therefore there was no benefit from the addition of immunotherapy with rIL-2 to standard chemotherapy.

Table 3 Projected dose intensity (*PDI*) and actual dose intensity of cisplatin, 5-FU and IL-2

Drug	PDI groups A and B	Mean actual dose intensity (% PDI)				
		Groups A and B	Group A	Group B	$\chi^{2\,a}$	*P*
Cisplatin	33.3 mg m^{-2} $week^{-1}$	88.6	88.8	88.3	0.012	0.913
5-FU	1666.6 mg m^{-2} $week^{-1}$	88.4	81.9	88.1	1.056	0.304
rIL-2	15. MIU m^{-2} $week^{-1}$			89.7		

[a] Yates-corrected χ^2-test group A versus group B

Dose intensity

As shown in Table 3, the actual dose intensity delivered was higher than 85% of the projected dose intensity. Moreover, there were no significant differences between the two treatment groups. Reduction of dose intensity was mainly due to the occurrence of leukopenia.

Loco-regional control of disease

Among all 28 patients, 7 (25%) [3/15 (20%) group A patients and 4/13 (31%) group B patients] were in CR after completing the treatment sequence and 15 (54%) [9/15 (60%) group A patients and 6/13 (46%) group B patients] were in PR. Thus 22 (79%) patients responded to therapy. The great majority of patients underwent radiation treatment as loco-regional therapy, which was delivered at a dose of 2 Gy/day five times/week with bilaterally opposed fields, which included the tumor primary site and upper neck. Four patients did not undergo loco-regional therapy because 3 died before therapy began and 1 refused the treatment.

Toxicity

The types and degrees of toxicity are shown in Table 4. G-CSF was given on a short-term basis, as requested, to allow for administration of full dose cycles. One patient (7%) of group B had grade 4 cardiac toxicity, which led to the patient's death. Grade 1–2 fever and grade 1–3 cutaneous toxicity (erythema) were recorded in 6 (43%) and in 2 (14%) patients, respectively, of group B, and were clearly attributable to IL-2 therapy.

Time to disease progression and overall survival estimates

Although the survival evaluation was not among the aims of our study, the Kaplan-Meier plots of time to progression and overall survival, updated to February 1997, are shown (Figs. 1, 2). At that date, 9/15 patients of group A were alive, whereas 8/13 patients of group B were alive. The mean overall survival was at least 9.1^+ months (range 1.9–16.6^+ months) for group A and at least 11.7 months (range 6.3–18^+ months) for group B. The mean time to progression was at least 7.6 (range 1.9–16.6^+) months for group A and 10.6 (range 6.0–18^+) months for group B.

Discussion

A number of new agents, such as vinorelbine, ifosfamide, edatrexate, piritrexim, paclitaxel and docetaxel,

Table 4 Numbers and percentages of patients with treatment-related toxicity

Type of toxicity	WHO score							
	Group A				Group B			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematological								
Leukopenia	2 (13%)	3 (19%)	2 (13%)	1 (6%)		3 (21%)	1 (7%)	
Thrombocytopenia	1 (6%)	1 (6%)	1 (6%)	1 (6%)	1 (7%)			
Anemia	1 (6%)	1 (6%)			1 (7%)	1 (7%)	1 (7%)	
Gastrointestinal								
Nausea/vomiting	3 (19%)	9 (56%)			6 (43)	6 (43%)	1 (7%)	
Stomatitis		5 (31%)	2 (13%)		1 (7%)	5 (36%)	3 (21%)	
Diarrhea	1 (6%)	1 (6%)	1 (6%)		1 (7%)		1 (7%)	
Cardiac								
Dysfunction								1 (7%)
Arrythmias						1 (7%)		
Hypotension						1 (7%)		
Phlebitis	1 (6%)				1 (7%)			
Cutaneous					1 (7%)		1 (7%)	
Fever					2 (14%)	4 (29%)		

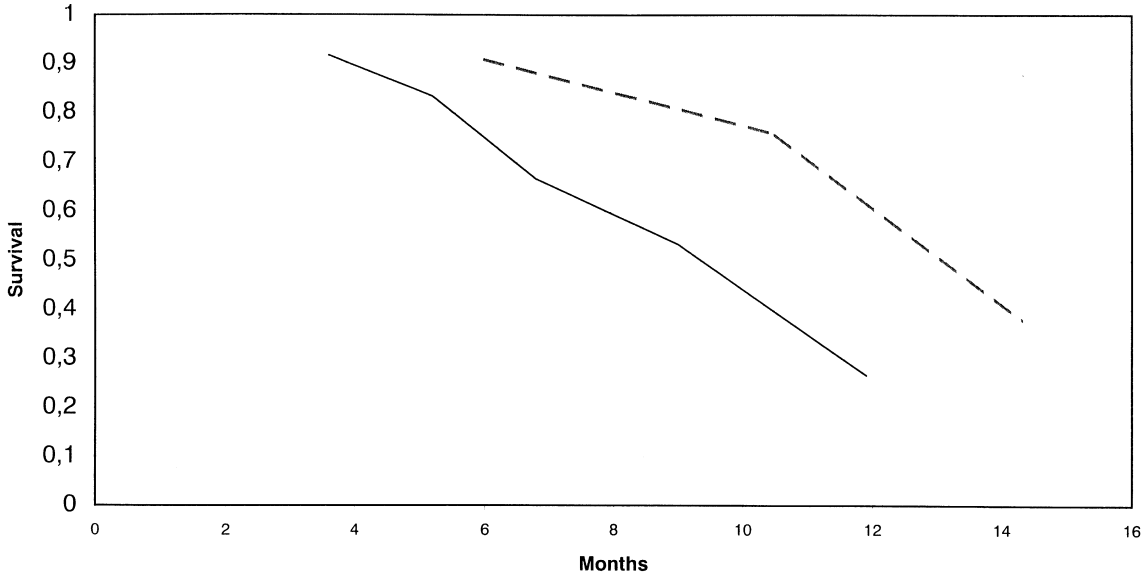

Fig. 1 Kaplan-Meier plot of time to disease progression. — Group A, – – – group B

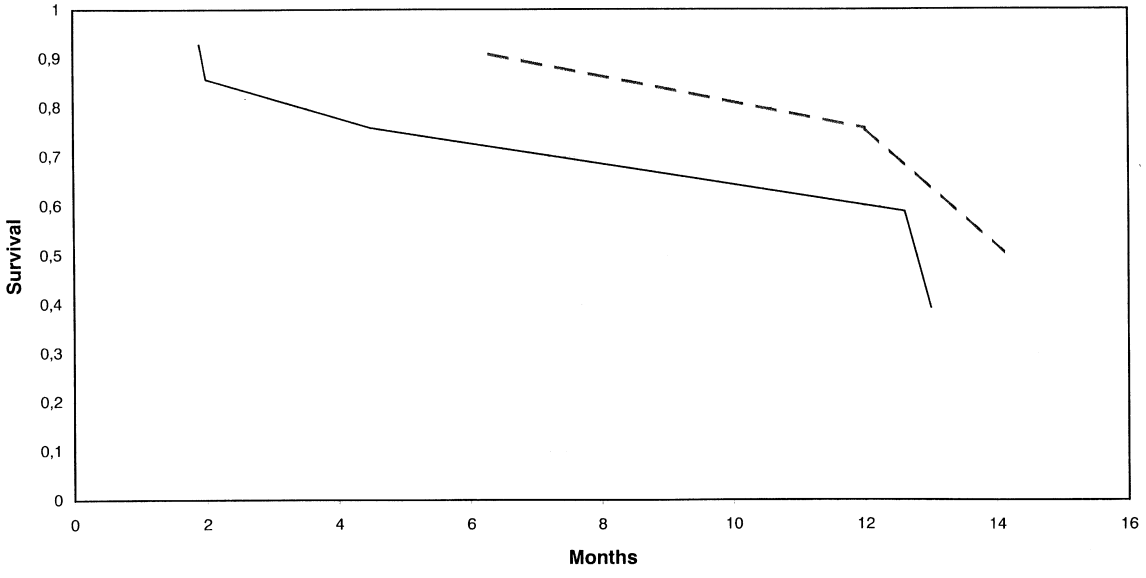

Fig. 2 Kaplan-Meier plot of overall survival. — Group A, – – – group B

have been recently identified that demonstrate significant single-agent activity in HNSCC, and some of them have been included in new regimens in phase II trials [19]. The most promising of these new regimens will need to be compared with standard regimens in randomized phase III trials. Till now no such randomized phase III trial has been reported.

The aim of our study was to improve the clinical effectiveness of what is the most active and most extensively used chemotherapy regimen for HNSCC: cisplatin + 5-Fu, by adding not a new drug but a biological response modifier, i.e. the cytokine rIL-2, which has been shown to be particularly promising in several studies in HNSCC (see Introduction).

The reasons for choosing rIL-2 from among the numerous cytokines potentially available in a chemo-immunotherapy approach to HNSCC were abundant: in a murine model human squamocellular carcinoma undergoes differentiation and finally regression after the peritumoral injection of IL-2 and lymphokine-activated killer (LAK) cells [22]; in man the regional injection of rIL-2 has been shown to be able to activate LAK cells as well as cytotoxic T cells in cervical lymph nodes [29]; in resected HNSCC a major inflammatory reaction and a greater infiltration with lymphocytes, eosinophils and plasma cells as well as a higher number of $CD25^+$ and DR^+ cells were found in patients treated with rIL-2 than in a control group; in a pilot study carried out by

Cortesina [6] on 10 patients with local recurrence of HNSCC, 200 IU natural IL-2 were injected into an anatomical site of the cervical region corresponding to the confluence of two draining lymphatics next to the jugular vein: the results were encouraging (3 CR, 3 PR, 4 SD), and the CR were seen in small recurrent lesions whereas no responses were found in patients who had previously undergone neck dissection. In a subsequent series of 20 recurrences, the same author obtained an approximate ORR of 20% (4/20 patients) with an identical technique [5]: the clinical ORR correlated with tumor infiltration by $CD25^+$ (IL-2 receptor) and LAK-1^- cells. Superimposable results were obtained [26] with laterocervical intralymphatic plus peritumoral injection of rIL-2 plus LAK cell infusion. In a recent ECOG trial carried out on 36 recurrent patients treated with various doses of rIL-2 administered by laterocervical and peritumoral injection (from 200 IU to 4 MIU), 2 PR were obtained; the maximal tolerated dose was 4 MIU/day [31]. In HNSCC patients the rIL-2 was shown to be able to induce LAK cells [39] as well as enhance NK activity and reverse the serum immunosuppressive activity of HNSCC patients [37]. Moreover, the rIL-2-activated LAK cells injected intraarterially were able to induce tumor regression in HNSCC patients [14].

Despite the rational approach documented above, previous abundant experimental evidence and some clinical evidence supporting its effectiveness, in our study the addition of rIL-2 was not able to improve the response rate of a standard chemotherapy regimen, such as cisplatin + 5-FU: the ORR (80% for group A and 77% for group B) and the CR rate (20% for group A and 31% for group B) of the two regimens were in the range of most previously published studies [3]. In fact, no statistical difference in response rate was found between the two groups although a slightly higher, but not statistically significant, CR rate was recorded in group B. One should consider that the actual dose intensity delivered in our study was very high and therefore the response rate obtained should have been the best achievable by the two regimens. We were not able to establish whether higher doses of IL-2 could have obtained better responses in group B, such as those obtained in our previously reported study [17]; however, it is worth noting, first, that the number of patients included in the previous study was very small (only 5 included in the arm containing IL-2) and therefore the results should not be applied generally to a more extended patient population and, secondly, that the toxicity recorded in that study, although not uniquely due to IL-2, was important, with 2 toxic deaths among 21 patients (1 toxic death in the arm containing IL-2).

Since the phase II study of Valone [30], our is, to our knowledge, the first phase III study comparing the combination cisplatin + 5-FU with the same drugs plus IL-2 for advanced-stage HNSCC patients; our response rates are better, apart from the different phases (II and III respectively) of the two studies, than those of Valone, which, however, included previously treated and metastatic patients. Our study may be compared also with those of Vokes, who added leucovorin [33] or leucovorin plus IFNα [35] as a second modulator to the cisplatin + 5-FU regimen, the ORR obtained by Vokes being slightly higher than those obtained by us.

In our study, after loco-regional treatment, 14 (50%) patients were in CR and 8 (29%) patients were in PR. Thus, 22 (79%) patients responded to therapy. We believe that there is no case for emphasizing the slight, non-significant CR difference between group A and group B, considering the small number of patients.

Both regimens were well tolerated. There were 2 toxic deaths (6.7%), 1 hematological in group A and 1 cardiac in group B. The cardiac toxicity was probably, though not certainly, related to IL-2 administration. Myelosuppression and gastrointestinal toxicity, mainly nausea/vomiting and stomatitis, were the most frequent toxicities. Severe stomatitis, which may be very distressing for such patients, was not frequent (13% for group A and 21% for group B). No significant difference was found in the types and degrees of toxicity between the two groups.

Though the data presented in this paper refer to an interim analysis, the calculated sample size of patients having been not yet reached, the projection of our present results suggests that it is highly improbable that a clinically significant difference between the two treatment groups will be achieved even when the calculated patient sample size is completed.

In conclusion, our study confirms that the combination of cisplatin and 5-FU does represent the "reference" regimen for HNSCC in the NAC setting. Moreover, in our opinion, NAC represents an ideal investigational tool with which to evaluate further the activity of new drugs or new treatment regimens in patients with head and neck cancer [33].

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