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Concomitant radio-chemotherapy for larynx preservation

Sergio Crispino,[1] P. Ghezzi,[1] A. Ribecco,[1] P. Ponticelli,[1] L. Lastrucci,[1] A. Colombo,[2] A. Ardizzoia,[2] F. Parmigiani,[2] M. Krengli,[3] G. Gambaro,[3] R. Taino[4] and F. Simeone[4]

[1]Medical Oncology-Radiotherapy, Arezzo, [2]Radiotherapy-Otolaryngology, Monza, [3]Radiotherapy, Novara, [4]Radiotherapy, Bergamo, Italy

Background: A pilot multicentric study of concomitant radio-chemotherapy was performed to evaluate the feasibility, the toxicity and larynx preservation rate in patients with previously untreated, resectable laryngo-pharyngeal squamous cell carcinoma, otherwise requiring laryngectomy ± pharyngectomy.
Materials and methods. Forty-two patients entered the study: radiotherapy was planned to a tumour dose of 70 Gy and chemotherapy was applied concomitantly, consisting of Cisplatinum and 5-Fluorouracil (bolus) or Carboplatinum and 5-Fluorouracil (continuous infusion) combination repeated every 3 weeks. In all but complete responders laryngectomy ± pharyngectomy and/or neck dissection was performed for residual disease.
Results: Toxicity was mild and no drug related deaths occurred. Complete response rate was 81% and, after salvage surgery, 93% of patients were considered disease free. After a median follow-up of 38 months, 53% of patients were alive and of these 88% with larynx preserved.
Conclusion: Concomitant radiochemotherapy seems to be a feasible strategy with acceptable toxicity for patients with laryngo-pharyngeal squamous cell carcinoma, otherwise eligible for total laryngectomy.

Key words: laryngeal neoplasms-drug therapy; laryngectomy

Introduction

During the last 20 years, chemotherapy has been used in the treatment of the larynx cancer, with various objectives and strategies. Pilot and multicentric randomized studies have been published on larynx preservation. Neoadjuvant chemotherapy has been the treatment of choice for the majority of these studies.[1-4] The use of concomitant radio-chemotherapy has been very limited. In September 1989, we started a pilot multicentric study of concomitant radio-chemotherapy in an integrated program of larynx preservation. The aim of this study was to evaluate the feasibility, the toxicity and the larynx preservation rate.

Correspondence to: Dr. Sergio Crispino, Centro Oncologico USL 8, Via F. Veneziana 17, I-52100 Arezzo, Italy.

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Materials and methods

Patients

From September 1989 to December 1994, 42 patients with biopsy proven, previously untreated laryngo-pharyngeal squamous cell carcinoma entered the study. All had tumors that were resectable and would require total laryngectomy +/- pharyngectomy according to the assessment of the attending surgeon. Thirty-two patients, with a minimum follow-up of 24 months, have been evaluated. The median age was 54 years (range 39-67), and the median Karnofsky performance status was 90 (range 70-100). All patients had adequate hematopoietic, hepatic and renal functions, and no coexisting medical problems to prevent full compliance with the study. The site of primary tumor and stage was as follows:

– larynx 16/32: (supraglottic: T3 N1-2 = 4; T4 N2-3 = 6; glottic: T3 N0-2 = 3; T2 N0 = 1; transglottic: T3 N0-1 = 2);

– hypopharynx +/- oropharynx 16/32 (T2 N0-2 = 3; T3 N0-1 = 6 ; T3 N2 = 5; T4 N1 = 2).

Treatment program

Radiotherapy was administered as standard treatment: 2 Gy daily 5 fractions per week up to a total dose of 70 Gy.

Concomitant chemotherapy:

– from 1989 to 1991: PF regimen = Cisplatinum 20 mg/m^2 IV days 1-4 and 5-Fluorouracil 200 mg/m^2 IV bolus days 1-4 ; cycles repeated every 3 weeks.

– from 1991 to 1995: CF regimen = Carboplatinum 75 mg/m^2 IV days 1-4 and 5-Fluorouracil 1000 mg/m^2 IV continuous infusion days 1-4 (96 hrs c.i.).

Clinical evaluation

Clinical evaluation was planned to be carried out 1 month after the completion of concomitant radio-chemotherapy. Patients in complete remission (CR) were followed-up, while patients with residual lesion on the primary tumor were candidates for a total laryngectomy +/- pharyngectomy. Patients with residual nodal lesions were eligible for neck dissection.

Results

The median dose of radiotherapy was 64 Gy and the median number of administered cycles of chemotherapy was 3.

Toxicity (RTOG-WHO): Grade 1-2 nausea and vomiting occurred in about 20% of patients, grade 2 anemia in 20%, grade 3 thrombocytopenia in 25%, grade 2 neuro-ototoxicity 25%, grade 1 nephrotoxicity 10%, aspirational bronchopneumonia 5%, neuro-nephro-ototoxicity occurred only in patients treated with the PF regimen. One patient had a miocardial infarction before the second cycle of CF. No drug-related deaths occurred.

Clinical results

After concomitant radio-chemotherapy 26/32 (81%) patients achieved CR. Three patients with residual disease of the primary tumor underwent total laryngectomy: microscopic disease was present in 2/3 of these patients, while only necrosis and fibrosis was evident in 1/3. One patient with residual nodal lesion underwent neck dissection and the histology showed only necrosis and fibrosis; one patient refused total laryngectomy, and one developed distant metastases before salvage surgery. At the end of the integrated program (concomitant radio-chemotherapy and salvage surgery), 30/32 (93%) patients were disease-free.

After a median follow-up of 38 months (24-68+ months), 17/32 (53%) patients were alive and disease-free. The larynx preservation rate was as follows: alive, disease-free with larynx/total: 15/32 (47%) patients; alive, disease-free with larynx/alive, disease-free: 15/17 patients (88%). Two patients out of 17 are alive, disease free without larynx. Fifteen patients out of 32 are dead: 6 with local or regional disease, 9 with distant metastases or a second primary cancer but with the larynx preserved and without evidence of locoregional disease; so the local and regional control were possible in 26/32 (81%) patients.

Conclusions

The use of radiotherapy and concomitant PF or CF chemotherapy, in patients with laryngo-pharyngeal cancer, eligible for a total laryngectomy, can be considered a feasible strategy and its toxicity seems acceptable. Both PF and CF regimens were used without major complications. Obviously, the administration of 5-Fluorouracil as IV continuous infusion was more complicated than 5-Fluorouracil IV bolus injection. In this study, the clinical advantage of the first modality of administration of 5-Fluorouracil compared to the second one remains to be established. Furthermore, also the clinical benefit of Carboplatinum *vs.* Cisplatinum in terms of toxicity, remains to be defined. Anyway, in both regimens a very high percentage of CR (81%) was obtained. The larynx preservation rate was very high.

Of the whole group of patients, 17/32 (47%) were cured of cancer and 15/17 (88%) had their larynx preserved. These results are highly competitive with those achieved with neoadjuvant chemotherapy.[1-4] Although concomitant radio-chemotherapy seems the best strategy to improve the locoregional control,[5,6] we think that only randomized studies can better define whether it is superior to neoadjuvant chemotherapy followed by radiotherapy or to radiotherapy alone in terms of toxicity, larynx preservation rate, survival and quality of life. Both, the appearance of distant metastases and second primary tumors, remain important problems to resolve, also with a concomitant treatment.

References

1. Pfister DG, Strong E, Harrison L et al. Larynx preservation with combined chemotherapy and radiation therapy in advanced but resectable head and neck cancer. *J Clin Oncol* 1991; **9:** 850-9.
2. Pinto HA, Jacobs C, Van Der Pas M et al. Long-term follow-up of organ preservation in advanced resectable head and neck cancer. *Proc ASCO* 1991; **10:** 690.
3. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991; **324:** 1685-90.
4. Lefebvre JL, Sahmoud T for the EORTC Head and Neck Cancer Cooperative Group. Larynx preservation in hypopharynx squamous cell carcinoma: preliminary results of a randomized study (EORTC 24891). *Proc ASCO* 1994; **13:** 912.
5. Al Sarraf M. Head and neck cancer: present status and future prospects of adjuvant chemotherapy. *Cancer Invest* 1995; **13:** 41-53.
6. Munro AJ. An overview of randomized controlled trials of adjuvant chemotherapy in head and neck cancer. *Br J Cancer* 1995; **71:** 83-9.