Radiol Oncol 1997; 31: 163-4.

Combined chemotherapy and radiotherapy in head and neck cancer: Hopes and facts

Jacek Jassem

Department of Oncology and Radiotherapy, Medical University of Gdañsk, Poland

Squamous cell carcinoma of the head and neck is one of the most common malignancies world-wide with more than 500,000 new cases projected annually.[1] Overall, only one-third of patients present with early local disease which may be successfully managed with either surgery or radiotherapy. The remaining two-thirds of patients already have locally advanced (T_3 or T_4) lesions and/or regional lymph node involvement (N_1 - N_3) at diagnosis.

Most of the patients with locally advanced tumor are treated with external beam irradiation with or without surgery. Despite the continued refinement of radiotherapy techniques, local tumor control remains a significant problem, with a recurrence rate of up to 60%. The majority of deaths from this malignancy are attributable to progressive locoregional disease. Many patients suffer significant morbidity from both, the therapy and cancer itself.

In an attempt to improve the outcome, many alternative strategies were tested within the last decades of which particularly common was adding chemotherapy to standard local treatment. Chemotherapy was applied before definitive local therapy (induction, neoadjuvant), after local treatment (adjuvant) or concomitantly with radiotherapy. The major expectation from the addition of chemotherapy is increasing the overall cure rate by either improved locoregional tumor control or by early elimination of micrometastases.

Correspondence to: Dr. Jacek Jassem, Department of Oncology and Radiotherapy, Medical University of Gdañsk, Dêbinki 7 st., 80-211 Gdañsk, Poland

Key words: head and neck neoplasms-drug therapy-radiotherapy; treatment outcome

UDC: 617.52/.53-08

Many phase II or pilot clinical trials, combining chemotherapy and radiation in a great variety of schedules, suggested a substantial benefit from the addition of chemotherapy. These claims, based on historical experiences, were usually subjected to various biases in favor of the new treatment and in general were not confirmed in randomized studies.[2] Of the three most common combined chemotherapy-radiotherapy approaches (induction, adjuvant, concomitant chemotherapy), a benefit in favor of chemotherapy, in terms of better local control and - to a lesser degree - prolonged survival was noted only with the last.[2,3] This improvement, however, was in most instances achieved at the expense of significantly increased toxicity of treatment. Chemotherapy usually enhanced acute local reactions (particularly mucositis), which led to a compromise in the dose of irradiation, interruption of treatment and increased number of treatment refusals. It is therefore possible that improved local control and survival might have been achieved at a similar, or even at lower level of toxicity, by simply increasing the total radiation dose or by employing altered fractionation regimens.

The lack of therapeutic gain from the addition of chemotherapy to radiation may be due to a number of reasons, including biological factors, increased rate of side effects and suboptimal methodology of clinical investigations. Head and neck cancers are a heterogeneous group of malignant tumors that differ considerably in their clinical manifestations, prognosis and therapeutic approaches. They are usually grouped together in clinical studies due to the small number of patients with individual tumor locations. This heterogeneity makes it difficult to evaluate chemotherapy as an independent variable. The most important factor, however, that influenced the outcome was insufficient patient number in

particular trials.[4] For this reason, most of the trials performed so far should be considered inconclusive rather than "negative", as usually claimed. Other components which might have influenced the reliability of published clinical reports are short duration of follow up and a large proportion of patients excluded from the analysis.

In spite of the disappointment with the current use of chemotherapy, there are still areas that deserve further investigation. One of them is the possibility of decreasing treatment morbidity by replacing mutilating surgery with organ-sparing procedures. This idea was tested in a few recent trials of which two attracted most interest,[5,6] addressing of the possibility to preserve the larynx. In both studies, patients with locally advanced laryngeal[5] or hypopharyngeal[6] cancers were randomized to either standard immediate surgery and postoperative radiotherapy or to induction chemotherapy followed by radiotherapy, which was applied only to responders to chemotherapy. Both studies demonstrated that the larynx preservation without compromising survival was possible in a proportion of patients. These studies, however, did not include a radiotherapy-only treatment arm and the extent to which induction chemotherapy contributed to organ preservation could not be therefore clearly defined. There are clinical data suggesting that larynx preservation could be achieved in a similar proportion of patients with the use of radiotherapy alone.[7] Further progress may also be expected from the application of newer radiotherapy techniques. e.g. hyperfractionation.[8,9] Anyway, the results of these studies may represent a major therapeutic achievement but warrant confirmation. Further exploration of this strategy may therefore be considered in patients with locally advanced laryngeal or hypopharyngeal cancer. It would be desirable to address the potential of organ preservation in concomitant chemoradiation protocols which have been proved to be more efficacious than induction chemotherapy.[10-12] It is also strongly advised to use, in the future studies, radiotherapy alone as a control arm, like in a currently running RTOG study.[13] Not only would such a design allow an assessment of the impact of chemotherapy, but it would also allow a comparative analysis of late side effects of radiation alone or combined with chemotherapy.

References

1. Boring CC, Squires TS, Tong T et al. Cancer statistics, 1992. *CA Cancer J Clin* 1992; **42:** 19-38.
2. Jassem J, Bartelink H. Chemotherapy in locally advanced head and neck cancer: a critical reappraisal. *Cancer Treat Rev* 1995; **21:** 447-62.
3. El-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region: a meta-analysis of prospective and randomized trials. *J Clin Oncol* 1996; **14:** 837-47.
4. Al-Sarraf M, Hussein M. Head and neck cancer: present status and future prospects of adjuvant chemotherapy. *Cancer Invest* 1995; **13:** 41-53.
5. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with laryngeal cancer. *N Engl J Med* 1991; **324:** 1685-90.
6. 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 Am Soc Clin Oncol* 1994; **13:** 283.
7. Harwood AR, Hawkins NV, Beale FA et al. Management of advanced glottic cancer: a 10 year review of the Toronto experience. *Int J Radiat Oncol Biol Phys* 1979; **5:** 899-904.
8. Horiot JC, Le Fur R, N'Guyen T et al. Hyperfractionated compared with conventional radiotherapy in oropharyngeal carcinoma: an EORTC randomized trial. *Eur J Cancer* 1990; **26:** 779-80.
9. Sánchiz F, Milla A, Torner J et al. Single fraction per day versus two fractions per day versus radiochemotherapy in the treatment of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1990; **19:** 1347-50.
10. Adelstein DJ, Sharan VM, Earle AS et al. Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer. *Cancer* 1990; **65:** 1685-91.
11. Merlano M, Corvo R, Margarino G et al. Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck: the final report of a randomized trial. *Cancer* 1991; **67:** 915-21.
12. Taylor SG, Murthy AK, Vannetzel JM et al. Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. *J Clin Oncol* 1994; **12:** 385-95.
13. RTOG 9111. Phase III randomized study of laryngeal preservation with CDDP/5-FU followed by radiotherapy vs concomitant radiotherapy and CDDP vs radiotherapy alone in patients with stage III/IV squamous cell cancer of the glottic and supraglottic. PDQ database, May 1994.