Redefining ‘state of the art’ in head and neck cancer

J. Bourhis*

Institut Gustave Roussy, 39 Rue Camille Desmoulins, Villejuif 94805, France

Head and neck cancers account for around 6% of cancers worldwide and present us with a number of treatment problems. Although treatment is often effective in early stage disease, a substantial proportion of patients present with advanced disease. Optimal disease management is hindered by the existence at presentation of co-morbidities and by the relatively high rate of second primary tumour development. When disease is locally advanced but still resectable, surgery is often mutilating and can deprive patients of basic functions, such as normal speech. Both radiotherapy and chemotherapy are associated with substantial toxicity, and the most common acute side effect is mucositis. Mucositis and difficulty with swallowing are particularly problematic and are a real issue for patients, potentially compromising nutrition and having a negative impact on the quality of life. Added to these are the potential problems associated with the late radiotherapy-related side effects, such as xerostomia, tooth decay, soft tissue fibrosis and, rarely, osteonecrosis.

This supplement contains the proceedings of a meeting held to discuss the current status of the treatment options for patients with head and neck cancer, to review recent treatment advances and to discuss potential future approaches. Professor Lefebvre discusses the scope of the problem of head and neck cancers and discusses the currently recommended standard treatment approaches for the different stages of disease. It is apparent to all of us in the field that despite the advances made in treatment, particularly over recent years, there is still a need to improve the outcome of patients. This is particularly true for patients with recurrent and/or metastatic disease for whom treatment options are limited, especially when disease progression occurs on standard cisplatin-based chemotherapy. Such patients have a dismal outlook, with a median survival of only around 4 months. As mentioned earlier, the need is not just to improve the efficacy of treatment, but also to improve its tolerability. To this end, novel therapeutic strategies are constantly being sought. Molecular targeted therapies offer physicians the opportunity to effectively block pathways essential to the development and progression of cancer without increasing the side effects associated with standard cytotoxic chemotherapy. In recent years, we have seen the ideal of targeted therapy become more of a reality, and increasing numbers of molecules have been identified as potential therapeutic targets for cancer. One such target, the epidermal growth factor receptor (EGFR), is the current focus of much attention.

The EGFR has been identified as playing an important role in the development and progression of a number of solid tumours, and a range of agents with differing mechanisms of action have been developed to target the receptor, several of which are showing significant activity in the clinical setting. The most studied of the EGFR-directed agents in head and neck cancers is the IgG1 monoclonal antibody (MAb) cetuximab (Erbitux®, Merck KGaA), which is directed at the extracellular ligand-binding site of the receptor. The EGFR tyrosine kinase inhibitors gefitinib and erlotinib have also demonstrated some activity. It is hoped that these agents will broaden the treatment opportunities in head and neck cancers.

Professor Harari provides a comprehensive overview of recent advances in radiotherapy for locally advanced disease. Radiotherapy has long been the treatment of choice for locally advanced disease. The introduction of altered fractionation regimens improves locoregional control compared with conventional fractionation, but survival benefits have yet to be convincingly demonstrated. In addition, accelerated fractionation schedules bring with them the problems of increased acute toxicity. A notable advance in radiotherapy is intensity-modulated radiotherapy (IMRT), which enables full radiotherapy dose delivery to tumour tissue but limits the exposure of healthy tissue. Although this is a relatively new technique and few long-term data are available, clinical interest in this approach is highlighted by the rapid adoption of IMRT by physicians, at least across the USA. The addition of cetuximab to radiotherapy is also discussed by Professor Harari. An international phase III study showed that the addition of cetuximab to conventional radiotherapy significantly improved locoregional control and prolonged survival [1]. What is particularly encouraging about these findings is that the efficacy conferred by cetuximab was achieved with minimal additive toxicity and no exacerbation of mucositis.

In another section, I discuss ways of enhancing chemotherapy in the treatment of SCCHN. Cisplatin, with or without 5-fluorouracil (5-FU), is the drug of choice in combination with radiotherapy for locally advanced disease. The platinum/infusional 5-FU regimen is by many clinicians also considered standard for patients with recurrent/metastatic disease who are able to tolerate this regimen. The benefit of adding chemotherapy to radiation therapy on patient survival compared with radiotherapy alone has been demonstrated by a large meta-analysis of trials, an update of which was reported recently [2]. Interestingly, the survival benefit was confined to the concomitant use of chemotherapy and radiotherapy (chemoradiotherapy). While

*Correspondence to: Dr J. Bourhis, Institut Gustave Roussy, 39 Rue Camille Desmoulins, Villejuif 94805, France. Tel: +33 1 4211 4998; Fax: +33 1 4211 5281. E-mail: bourhis@igr.fr

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the utility of neoadjuvant chemotherapy in organ preservation is recognised, data from the meta-analysis failed to confirm a survival benefit for this approach. However, encouraging data from studies involving taxane-based chemotherapy have rekindled interest in the potential survival benefits of neoadjuvant chemotherapy and this approach is once more being actively pursued. Cetuximab potentiates the effects of chemotherapy, and results from a number of clinical trials demonstrate the significant activity of cetuximab in combination with chemotherapy in the treatment of recurrent and metastatic disease both in the first-line setting and for platinum-resistant disease. Interestingly, the response rate observed with cetuximab monotherapy was in line with that achieved with cetuximab/cisplatin combination therapy in the platinum-resistant setting [3].

Professor Vokes presents treatment options in the light of recent therapeutic innovations and discusses the issues that need to be addressed to enable treatment to be improved further. Chemoradiotherapy has superseded radiotherapy alone as the standard treatment of choice in the post-surgical setting, when organ preservation is required and in unresectable disease. With the emergence of altered fractionation regimens and new active chemotherapeutic agents, the optimal chemoradiotherapy regimens now need to be defined. The potential survival benefits of neoadjuvant chemotherapy observed with taxane-based regimens has prompted renewed investigation into this treatment approach. Professor Vokes describes the design of a randomized trial to investigate the benefits of the addition of paclitaxel/cisplatin neoadjuvant chemotherapy to paclitaxel/5-FU/hydroxyurea/radiotherapy. Finally, Professor Vokes discusses the data available with EGFR-targeted therapies and highlights the importance of the effective integration of these agents into current management strategies.

As the papers in this supplement attest, we have undoubtedly made progress in the management of head and neck cancers. However, as in all areas of oncology, longer survival, fewer treatment-related side effects and better quality of life are goals we continue to strive for. While the place of molecular targeted therapies in the treatment spectrum for different stages of SCCHN remains to be determined, these therapies will probably change the way we treat some of these head and neck cancers.

References

