18.1 Introduction

Squamous cell carcinomas of the head and neck (SCCHN) are a heterogeneous group of malignancies that originate in the epithelium of the nasal cavity, sinuses, pharynx, oral cavity, and larynx. They are frequently diagnosed at advanced stages with extension of the primary tumor to adjacent structures and/or regional spread to neck lymph nodes. Since SCCHN and its treatment can affect organs and systems critical for important functions, such as speaking, breathing, and swallowing, patients with SCCHN may develop a variety of symptoms and impairments, including mouth or neck pain, difficulties in chewing and swallowing resulting in malnutrition and aspiration, hoarseness or loss of natural voice, problems in breathing, head and neck deformities, and others. Given the risk for potential functional deficits from concomitant chemoradiotherapy has been shown to improve locoregional control, organ preservation, and/or survival over radiotherapy alone and has emerged as a standard treatment for patients with locally advanced squamous cell carcinoma of the head and neck.

The addition of chemotherapy to radiotherapy can worsen acute radiation-induced toxicities, including mucositis and dermatitis, and result in chemotherapy predominantly-related toxicities, such as myelosuppression, neuropathy, nausea and vomiting.

As treatment has been intensified, it becomes increasingly important to measure and address the impact of treatment-related toxicities on quality of life parameters.

The incorporation of targeted systemic agents, such as the epidermal growth factor receptor inhibitors, and of radioprotectants into combined modality treatments offers the potential for improving the risk to benefit ratio.

Future clinical research should focus on how to ameliorate acute and late treatment-related toxicities and improve quality of life while maintaining therapeutic efficacy.
potentially curative treatment, not only cure but organ preservation, functional outcomes, and quality of life (QOL) are of foremost importance in the management of patients with SCCHN.

Therapeutic options for the treatment of locally advanced SCCHN have evolved over the past two decades as a result of developments in the area of combined modality strategies. Historically, standard therapy for locally advanced SCCHN involved surgical resection with or without postoperative radiotherapy for resectable disease or radiation therapy alone for unresectable tumors. In an effort to increase the probability of organ preservation and survival, chemotherapy was evaluated as a component of combined modality approaches. The contribution of induction, concomitant, and/or adjuvant chemotherapy was studied in a large number of phase III randomized clinical trials. On the basis of this cumulative experience, concomitant chemoradiotherapy (CRT) emerged as a standard treatment for improving survival and/or achieving organ preservation in locally advanced SCCHN. However, with treatment intensification, mostly related to the addition of chemotherapy to radiotherapy in a concurrent fashion, complications of treatment are seen in increased frequency. This chapter aims to concisely review the efficacy and toxicity of current combined modality approaches with a focus on functional outcomes and the potential impact on QOL.

18.2 Chemotherapy in Multimodality Treatment

Patients with locally advanced SCCHN (i.e., AJCC stages III/IVA–B) have a potentially curable disease that requires multidisciplinary evaluation and management. A major step forward in the treatment of locally advanced SCCHN was the introduction of the concurrent administration of chemotherapy and radiotherapy. Numerous randomized clinical trials demonstrated that concomitant CRT yields improved locoregional control and/or survival than either radiotherapy alone or the sequential administration of chemotherapy and radiotherapy (Table 18.1). A meta-analysis of individual patient data from nearly 11,000 participants in 63 trials conducted between 1965 and 1993 (Meta-analysis of Chemotherapy in Head and Neck Cancer [MACH-NC]) demonstrated that the addition of chemotherapy to locoregional treatment, as induction, concomitant, or adjuvant treatment, confers an absolute survival benefit of 4% at 5 years (Pignon et al. 2000). Most of the benefit was seen with concomitant CRT; however, there was a relatively large heterogeneity in this subgroup of trials. An updated analysis that included 24 additional studies and a total of 9,615 patients treated with concomitant CRT confirmed that it produces an absolute survival improvement of 8% at 5 years (Bourhis et al. 2004). The survival advantage with concomitant CRT over radiotherapy alone was predominantly a result of improved locoregional control, whereas only a minor impact on distant recurrence was evident. The survival benefit documented in multiple randomized clinical trials and meta-analyses supported the use of concomitant CRT as a standard-of-care treatment of stage III/IV SCCHN (Argiris et al. 2008).

Although many regimens of CRT have been used, platinum-based concomitant CRT is widely accepted as standard. High-dose cisplatin (100 mg m−2 every 3 weeks for three cycles) is the regimen that has been studied the most and has yielded positive results in multiple cooperative group phase III trials in locally advanced SCCHN (Adelstein et al. 2003; Al-Sarraf et al. 1998; Bernier et al. 2004; Cooper et al. 2004; Forastiere et al. 2003). Cisplatin or carboplatin plus 5-fluorouracil (5-FU) has also been extensively utilized (Calais et al. 1999; Wendt et al. 1998).

Induction chemotherapy with the addition of taxanes (docetaxel or paclitaxel) to cisplatin and 5-FU was shown to improve survival (Hitt et al. 2005; Vermorken et al. 2007; Posner et al. 2007) or organ preservation outcomes (Calais et al. 2006) over cisplatin and 5-FU alone in phase III randomized clinical trials. This led to a renewed interest in the role of induction chemotherapy in locally advanced SCCHN. A number of ongoing randomized trials are evaluating the potential survival advantage when cisplatin, docetaxel, and 5-FU are added to concomitant CRT. As regimens that incorporate induction are increasingly utilized, the potential of cumulative or repeated toxicities over a prolonged treatment period should be taken into consideration (Trotti et al. 2007).

18.3 Organ Preservation Considerations

Major factors affecting the choice of primary treatment modality include tumor resectability and the desire for organ preservation as well as the ability of