



## Criteria for eligibility to cisplatin in the curative treatment of head and neck cancer: Consensus opinion from a panel of experts

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### ABSTRACT

Squamous-cell carcinoma of the head and neck (SCCHN) is an important problem in Brazil, where epidemiological and socioeconomic features often create barriers to the implementation of combined modalities with curative potential. Cisplatin improves the efficacy of radiotherapy in the adjuvant treatment of localized SCCHN and in the definitive therapy of locally advanced disease. However, the addition of high-dose cisplatin to radiotherapy increases treatment toxicity and is not always warranted. A panel of experts convened in Sao Paulo, Brazil, for discussions and recommendations regarding the use of high-dose cisplatin in combination with radiotherapy in SCCHN. In addition to discussing their professional experience, panel members used the current literature to provide evidence-based, practical recommendations regarding sociodemographic or medical criteria that may preclude safe administration of cisplatin. It is hoped that the application of these recommendations in clinical practice may improve therapeutic results in Brazil and other countries with similar health-care environments.

### 1. Introduction

With nearly 700 thousand new cases and 400 thousand deaths per year, squamous-cell carcinoma of the head and neck (SCCHN) is more frequent in developing countries, and currently accounts for 5% of malignancies worldwide (Ferlay et al., 2015). Central and South America are characterized by high incidence rates for head and neck cancer (Perdomo et al., 2016). Such rates are especially high in Brazil, where oral cavity and larynx tumors combined represent the second most frequent tumor type among men, with slightly larger number of estimated new cases every year than lung cancer (Brasil. Ministério da Saúde. Instituto Nacional de Câncer, 2018). Although scientific advances in SCCHN have been slower than those observed in other

subspecialties of oncology, multidisciplinary management, organ preservation, the recognition of the biologic diversity of different types of SCCHN, and the advent of effective systemic therapies have all brought incremental improvements over the past two decades (Rischin et al., 2015). Moreover, the recognition of the role of chemotherapy, especially high-dose cisplatin, as an adjunct to radiotherapy in the treatment of patients with resectable and locally advanced disease has been an important milestone in SCCHN (Pignon et al., 2009). However, the addition of high-dose cisplatin to radiotherapy increases treatment toxicity and may not be warranted in some patients, and it has been suggested that only about half of the patients are able to receive the planned three cycles of high-dose cisplatin (Bernier et al., 2004). In addition to acute toxicity, such as nausea, vomiting, renal dysfunction,

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myelosuppression, transaminase and bilirubin elevation, hypersensitivity reactions and other less frequent events, the risk of long-term complications from the use of high-dose cisplatin should always be borne in mind. Such late toxicities are usually seen in patients treated with chemoradiation protocols, and include dysphagia, xerostomia, hypothyroidism, ototoxicity, and osteoradionecrosis (Rivelli et al., 2015).

Brazil is a country where socioeconomic features often create barriers to the widespread implementation of combined modalities with curative potential (Sanabria et al., 2010). Moreover, there is insufficient local data that may inform decisions about individual treatment modalities, especially systemic therapy (de Castro et al., 2007). Thus, in March 2017 a panel of experts convened in Sao Paulo, Brazil, to discuss and provide recommendations regarding the safe use of high-dose cisplatin in combination with radiotherapy in oral cavity, oro- and hypopharynx, and larynx squamous-cell carcinomas, here named as SCCHN. The results of that panel, presented in this paper, aim at informing health-care providers caring for patients with SCCHN in Brazil and in other countries with similar socioeconomic environments.

## 2. Panel methodology

### 2.1. Panel composition and scope

The expert panel consisted of 10 invited members and one moderator, all of which involved on a daily basis in the management of patients with SCCHN. Members consisted of nine medical oncologists and one head and neck surgeon, all from Brazil. Such individuals practice in five of the 27 federated units from Brazil, which are home to nearly 53% of the current Brazilian population (Brasil. Instituto Brasileiro de Geografia e Estatística, 2018). The expert discussions were moderated by one international expert (AC), who had the explicit function of coordinating the panel with the goal of formulating the recommendations after sufficient consensus had been reached. Discussions were restricted to the literature pertaining to the cisplatin dose of 100 mg/m<sup>2</sup> every 3 weeks used to treat resectable SCCHN in the adjuvant setting and unresectable SCCHN in the definitive setting, including larynx-preservation strategies, always in combination with conventional-fractionation radiotherapy delivered by linear accelerators (Bernier et al., 2004; Cooper et al., 2004; Adelstein et al., 2003; Forastiere et al., 2003). Therefore, the discussion and recommendations that follow do not pertain to the use of cisplatin as a component of neoadjuvant therapy, to lower doses of cisplatin, or to carboplatin. Moreover, since there are some concerns regarding the use of high-dose cisplatin concurrently with radiotherapy following cisplatin-based neoadjuvant chemotherapy (National Comprehensive Cancer Network, 2017), this particular scenario is excluded from the recommendations below.

### 2.2. Session format and discussions

The expert panel was held during one morning. The international expert presented an overview of the literature regarding the eligibility to, and risks from, cisplatin use in combination with radiotherapy. This presentation, which allowed for the identification of key patient features potentially influencing the eligibility to high-dose cisplatin, was followed by discussions on how such features may be used in decision-making. For each of the patient features potentially influencing the eligibility to high-dose cisplatin, members of the panel discussed their professional experience and the current scientific literature with the goal of providing evidence-based, practical recommendations for the safe administration of this agent. Although an attempt was made to classify each potential contraindication to the use of high-dose cisplatin as absolute or relative, no formal systems were applied to appraise the literature or to ascertain levels of evidence for the recommendations, which represent the consensus opinion of panel members. The

designation of relative contraindication is applied to situations for which extreme caution is required during therapy, with an increased frequency and intensity of patient monitoring in comparison with the routine use of high-dose cisplatin.

Regarding the selection of the studies considered by the experts to support their opinions, the following terms were used: head and neck cancer, guidelines, expert opinion, cisplatin, chemoradiotherapy, criteria, toxicity, unsuitability. The experts selected the studies they considered relevant, based on the impact of the journal, the statistical and study design, and the robustness of the results. In addition, the experts considered the EHNS-ESMO-ESTRO squamous cell carcinoma of the head and neck clinical practice guidelines.

### 2.3. Role of the sponsor and panel members

The expert panel was sponsored by Merck Brazil. The meeting sponsor selected and invited panel members but had no direct influence on panel recommendations. The current authors vouch for the entirety of the recommendations and discussions presented herein.

## 3. Panel Recommendations

### 3.1. Initial assessment

An overarching principle shared by panel members is that treatment decisions should be individualized and based on the collective assessment of all elements displayed in Table 1. Ideally, patients with SCCHN should be managed by a multidisciplinary team that involves at least a head and neck surgeon, a radiation oncologist, and a medical oncologist. Close communication among these specialists is of paramount importance and cannot be overemphasized. Furthermore, it is desirable that a multidisciplinary team of other health-care professionals (e.g., dentists, nurses, psychologists, dietitians and speech therapists, among others) take part in treatment decisions.

Before treatment initiation, patients with SCCHN should be assessed as recommended by expert consensus, such as the National Comprehensive Cancer Network (NCCN) group (National Comprehensive Cancer Network, 2017). In addition to the usual medical, surgical, dental and nutritional assessment recommended for such patients (National Comprehensive Cancer Network, 2017), those in whom high-dose cisplatin is contemplated should ideally undergo an evaluation of their cardiac function and a baseline audiogram. Moreover, attention should be paid to the socioeconomic setting and the family support available to each patient, because these are critical factors in ensuring the safe use of high-dose cisplatin and radiotherapy (Sanabria et al., 2010). Social considerations include patient understanding and willingness to undergo the recommended treatment, family and social support during and after such treatment, daily commute to treatment centers, and health-insurance coverage. Moreover, socially vulnerable and institutionalized patients should receive special attention, as treating these individuals according to state-of-the-art guidelines is often not feasible. Likewise, the patient's ability to resume professional activities after treatment should be considered, because even in developed countries only about 50% of patients are able to return to work after 2 years (Isaksson et al., 2016). Data from Brazil suggest that nearly one-third of patients with SCCHN who are alive and disease-free 2 years after treatment are unable to resume their professional activities (Vartanian et al., 2006). Additional factors to be considered in the baseline assessment are the control of substance use, including smoke, alcohol, and illicit drugs, especially in view of the association between the continuation of such use and worsened outcomes, including the risk of second primary neoplasms (Franchin et al., 2003; Sandoval et al., 2009; Kikidis et al., 2012).

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