



## Review

# Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: A literature review



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## SUMMARY

Toxicities resulting from platinum based chemotherapy in head and neck cancer is a cause for much concern. There is a lack of clinical criteria for defining these patient populations, which has posed serious problems associated with increased morbidity and consequently an adverse effect on patients' quality of life. In addition, there is a lack of consensus on clinical criteria for defining such patient populations, who may be unsuitable for concurrent chemoradiotherapy. A group of experts in the field of head and neck cancer from the Asia Pacific Region convened in August 2014 in Korea to discuss the development of a set of clinical criteria in order to fill the knowledge gap and provide a reference tool for head and neck oncologists. This paper reports the final output from this meeting and the accompanying literature review, with the aim of aiding clinical decision making with the help of some clinical criteria to identify platinum unsuitable patient populations in head and neck cancer management. Some alternative treatment options are also discussed in this paper.

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## Introduction

## Background

Squamous cell carcinoma of the head and neck (SCCHN) accounts for 6% of all malignancies. There are an estimated 686,000 new head and neck cancer cases and 376,000 related deaths per year worldwide [1]. The majority of SCCHN patients

are diagnosed with loco-regional disease, while 10% of patients present with metastatic disease from the start [2].

The MACH-NC analysis (meta-analysis of chemotherapy in head and neck cancer) demonstrated a 6.5% absolute improvement in 5-year overall survival with concurrent chemo-radiotherapy (CCRT) over radiotherapy (RT) alone. Concurrent high-dose cisplatin (100 mg/m<sup>2</sup> on days 1, 22 and 43 during RT) was identified as the most effective regimen [3]. Definitive CCRT, with high-dose cisplatin, is therefore regarded as the preferred choice in the European and NCCN clinical practice guidelines for the treatment of fit patients with loco-regionally advanced SCCHN (LA-SCCHN) [4,5].

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However, platinum-based CCRT is hampered by acute and late toxic effects, and in particular the late toxicity has major implications for the quality of life of the cancer survivors. This becomes an even more severe problem when cisplatin-based induction chemotherapy is followed by cisplatin-based CCRT. Issues relating to cumulative toxicity concerns with this latter approach place restrictions on its routine use as a standard form of treatment in LA-SCCHN. It is worthy of note that in a multivariate analysis of three studies in which patients were treated with CCRT, older age, advanced tumor stage, larynx/hypopharynx primary site, and neck dissection following CCRT proved to be strong independent risk factors in predicting severe late toxicity and complications [6]. Methods to reduce the toxicity of cisplatin-based CCRT include, among others, better radiation targeting, the use of newer radiotherapy techniques, and alternatives to the use of high-dose cisplatin. Based on the earlier mentioned MACH-NC meta-analysis the use of carboplatin/5-fluorouracil is an accepted alternative, both in Europe and in the US. For all other approaches, there is currently uncertainty regarding the best choice for concomitant agents. That is also the case for patients in whom cisplatin may be contraindicated, such as in those with pre-existing auditory problems, peripheral neuropathy and/or renal dysfunction. However, sufficiently large phase III trials of low-dose weekly cisplatin or other cytotoxic agents versus standard high-dose cisplatin during RT are lacking, and therefore these approaches have not reached the same level of recommendation.

As for the use of cetuximab as an alternative to high-dose cisplatin, the recommendations in Europe differ from those formulated in the NCCN guidelines. There has been no randomized phase III trial reported that compares cetuximab/RT with cisplatin-based CCRT and the only data available are those reported from a phase III trial, comparing cetuximab/RT with RT alone [7], and from a randomized phase II study, comparing cetuximab/RT with cisplatin-based CCRT after cisplatin-based induction chemotherapy [8]. In addition, a recently published literature-based meta-analysis on platinum-based CCRT versus cetuximab/RT showed significantly better 2-year results with respect to overall survival, progression-free survival and loco-regional control [9]. The lack of sufficient data addressing these issues confounds decision making. Yet, the choice for the most optimal treatment for an individual patient is a critical issue and therefore a better selection of patients who might need less aggressive therapy versus those who might need more is another important area of research [10–12].

With quality of life being an important aspect while considering treatment options, a risk based approach toward appropriate patient selection is crucial as not all patients may require exposure

to highly cytotoxic therapy, e.g. young patients with HPV (human papillomavirus) positive oropharyngeal cancers and no history of regular smoking [13].

As may be seen from the NICE UK guidelines, knowledge gaps exist (Table 1) in defining criteria for platinum intolerance or increased toxicity in at-risk patients with LA SCCHN [14].

Given to understand the potential gaps in guidelines (Table 1) versus their clinical interpretation, we may explain the reason for some cause for ambiguity and likelihood of misinterpretation of these guidelines when approaching patients in the management of head and neck cancer. In the absence of any literature that clearly defines the category of platinum unsuitable patients, it therefore becomes essential for the formulation of consensus guidelines among head and neck experts after appropriate literature review in establishing clear and definitive clinical criteria in this group of patients with LA-SCCHN.

#### Summary of short and long-term impact of treatment related toxicities

Cisplatin, or cis-diamminedichloroplatinum (II) can react in vivo, binding to and causing crosslinking of DNA, which ultimately triggers apoptosis [15]. As for the metabolism of cisplatin, total platinum declines tri-exponentially ( $t_{1/2\gamma} = 4-6$  days) and its half-life will further increase later on. Free platinum, which is central to the anti-tumor activity, declines in biphasic manner ( $t_{1/2\beta} = 40$  min). Maximum platinum levels of 0.51–0.58  $\mu\text{g/ml}$  (in 90–150 min) in red blood cells (RBCs) can be reached after administration of 100  $\text{mg/m}^2$  cisplatin. About 30% can be excreted from the body within 24 h [16,17].

Most toxicities are dose and schedule dependent, with shorter infusions inducing earlier and more severe toxicity than slow infusions, suggesting that some of the toxicities are peak-dose dependent. Nausea and vomiting are common. Renal insufficiency is cumulative, can be ameliorated by hydration, but cannot be completely prevented. The symptoms of neurotoxicity typically occur after a cumulative dose of 300  $\text{mg/m}^2$ ; and the symptoms begin and often progress up to 4 months after stopping cisplatin; in 30–50% of patients neurotoxicity is irreversible. Ototoxicity is cumulative and irreversible. Other toxicities include myelosuppression, liver toxicity with increased transaminases, and pyrexia. Rare toxicities may comprise hypersensitivity, visual impairment, hemolytic anemia, Raynaud's syndrome, hypertension, cardiac events and microangiopathy.

All reasonable precautions should be taken when using cisplatin, such as avoiding use of other nephrotoxic drugs e.g. aminoglycosides, monitoring electrolytes ( $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$ ), and maintaining high urine flow during therapy. Aggressive

**Table 1**  
Gaps in existing criteria.

Excerpt from NICE guidelines	Gaps in criteria
1.1 Cetuximab in combination with radiotherapy is recommended as a treatment option only for patients with LA SCCHN whose Karnofsky performance status (KPS) score is 90% or greater and for whom all forms of platinum based chemo-radiotherapy treatment are contraindicated	1. Recommendation 1.1 mentions platinum unsuitable patients, but fails to define clear criteria for contraindications and intolerance to platinum observed in practice
1.2 Patients currently receiving cetuximab in combination with radiotherapy for the treatment of LA SCCHN who do not meet the criteria outlined in section 1.1 should have the option to continue therapy until they and their clinicians consider it appropriate to stop	2. Recommendation 1.1 states that patients with a KPS score of $\geq 90\%$ are eligible for cetuximab plus radiotherapy (RT), and Recommendation 1.3 further stresses the use of this scoring method. However in real practice, it is patients with poor PS who receive cetuximab + RT
1.3 When using Karnofsky performance status score, clinicians should be mindful of the needs to secure equality of access to treatment for patients with disabilities. Clinicians should bear in mind that people with disabilities may have difficulties with activities of daily living that are unrelated to their prognosis with respect to cancer of the head and neck. In such cases clinicians should make appropriate judgment of performance status taking into account the person's usual functional capacity and requirement for assistance with activities of daily living	3. Patients who have received cisplatin based induction therapy may be not suitable for concomitant chemo-radiotherapy in the definitive phase due to cumulative toxicity. However this commonly practiced protocol is not covered in the Recommendations

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