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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.

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^2 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 ($t1/2\gamma = 4–6$ days) and its half-life will further increase later on. Free platinum, which is central to the anti-tumor activity, declines in biphasic manner ($t1/2\beta = 40$ min). Maximum platinum levels of 0.51–0.58 μg/ml (in 90–150 min) in red blood cells (RBCs) can be reached after administration of 100 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 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 (Mg^{2+} and 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 $\geqslant$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

antiemetic treatment, i.e. the triple regimen [5-HT3 RAs (5-hydroxytryptamine receptor antagonists), corticosteroids, and NK1RAs (neurokinin 1 receptor antagonists)] can be helpful; and full high dose of cisplatin is usually administered only in case of a creatinine clearance (CCR) of $\geqslant$60 ml/min.

A study in which cisplatin was administered at different dosages by rapid infusion revealed that the binding of platinum to both plasma and proteins and RBCs in vitro (using patients' own blood) was slow, biphasic, and irreversible [16]. Another study compared three different infusion schedules, i.e. the rapid infusion, 3-hour infusion or 24-hour infusion, while the same dose of cisplatin was used throughout. Peak plasma concentrations differed substantially (both total and free platinum species) and, as mentioned earlier, this may have implications with respect to some of the toxicities that patients may experience. On the other hand, the area under the concentration-time curves (AUC) of the free platinum species (the active component) proved to be comparable to each other and independent of the infusion schedule, when cisplatin was given at the same dose [18]. This might suggest that irrespective of the infusion schedule, cisplatin administered at the same dose would produce the same level of anti-tumor activity. Prolonged infusions may therefore lead to less toxicity than rapid infusions.

A study on ototoxicity showed that the incidence of audiographic changes increased with increasing cumulative cisplatin dose independent of the treatment schedule. The incidence correlated with the daily dose ($P = 0.0037$) and changes were more severe after single high doses [19]. Patients with preexisting hearing loss were at higher risk of suffering from deafness at a later time. In that study it became evident from an analysis performed in patients treated with the so-called LD5 regimen, i.e. 20 mg/m^2/day for 5 days, that age did have an influence on the development of ototoxicity ($P = 0.041$). Older patients were more susceptible to more severe ototoxicity (Fig. 1).

Long-term toxicity in patients after cisplatin-based chemotherapy, especially cardiovascular risk factors [20], does take place as cisplatin can adhere to all tissues for a long time (Fig. 2) [21]. Even 20 years after cisplatin-based chemotherapy, platinum can still be found in plasma.

Objectives

In view of the above literature review, existing PK-PD (pharmacokinetic-pharmacodynamic) data from basic and extensive research and the unmet need for clinical criteria to define platinum unsuitable patient populations, an Expert Panel meeting was held in South Korea to identify patient populations who may be ineligible for platinum based therapy or at high risk of severe acute and late toxicities after platinum based treatment in SCCHN.

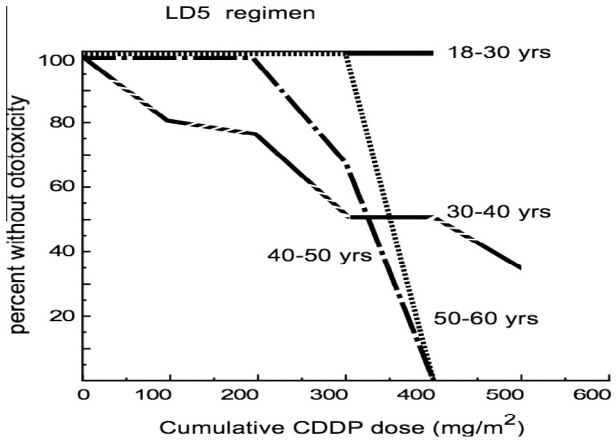

Fig. 1. Incidence of audio-graphic changes in relation to cumulative cisplatin dose in patients of different age categories.

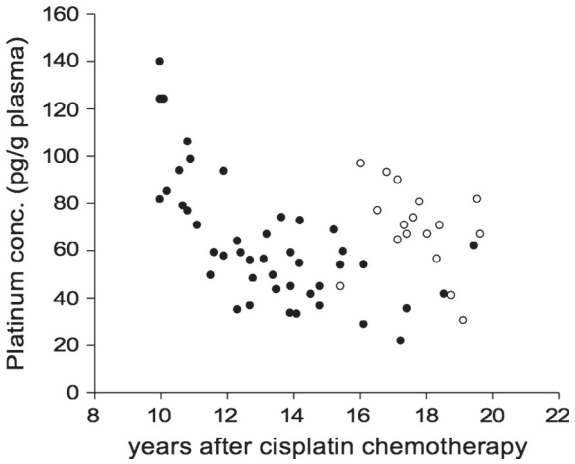

Fig. 2. Circulating plasma platinum >10 years after cisplatin treatment for testicular cancer.

Platinum unsuitable patients are defined as those in whom platinum based chemotherapy is either contraindicated or leads to increased risk of toxicity. Correspondingly, the clinical practice recommendations developed in this paper will focus on: (1) criteria for defining platinum intolerance and contraindications; (2) criteria for defining at-risk populations who receive cisplatin.

Methodology

Structure of the expert panel meeting

The Panel members were composed of experts with substantial experience in medical, radiation and surgical oncology from Belgium, India, Korea, Hong Kong, Mainland China, Australia, Vietnam, Taiwan and Thailand. They convened to discuss the clinical recommendations and criteria for defining platinum ineligibility in patient populations with head and neck cancer. The Expert Panel meeting followed the Delphi principle of consensus development, wherein the experts were adequately updated on the topic, with a summary of the available literature. In addition, the experts were given room to exchange clinical experience to achieve a practical and pragmatic solution to the unmet needs identified.

Method of discussion

Following a presentation on evidence and research outcomes to identify platinum unsuitable patient populations in head and neck cancer, the Expert Panel was split into two groups (Fig. 3) in order for panel members to list clinical criteria for, respectively, contraindications to platinum (Group A) and cases at high risk of platinum toxicities (Group B). It was advised that a balance should be achieved between literature evidence and real-life clinical practice.

Method for forming consensus/recommendations

Two representatives, nominated by their respective groups, presented back the results to the Panel on behalf of Group A and B, and a senior distinguished oncologist moderated the Panel discussion session to spark in-depth debate on various contentious issues. The concept of absolute contraindications was put forward to avoid overlap between Group A and B.

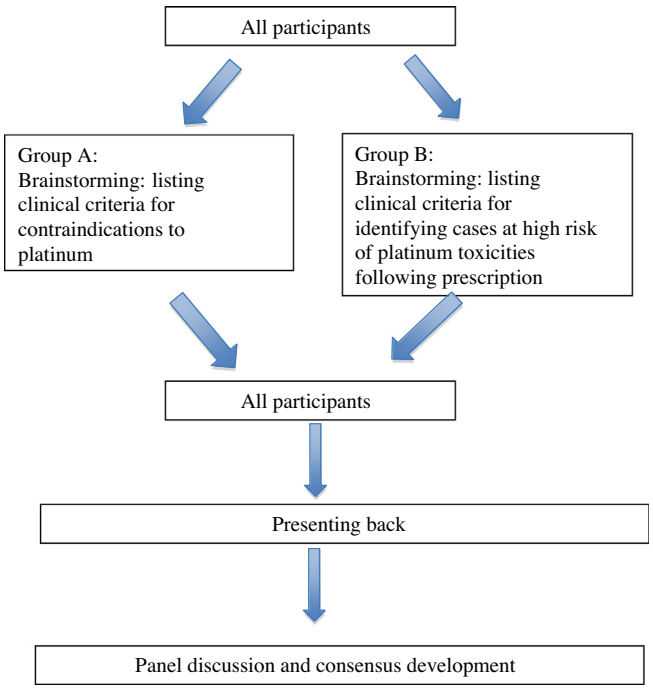

Fig. 3. Workflow for group discussion.

The absolute contraindication means an event that could cause life-threatening conditions. A procedure or medication that falls under this category should be avoided. On the other hand, high risk means that caution should be taken when a procedure or medication is being used.

Consensus and recommendations

In accordance with the findings from the literature review the Panel members listed as many items as possible by brainstorming. These items were re-categorized during the panel discussion session following reaching an agreement among Panel members. The final output of Group A and B is summarized in Tables 2 and 3.

Criteria for contraindications to platinum exposure

Consensus was reached that cisplatin should not be used in patients who have the following characteristics: a performance status ECOG (Eastern Cooperative Oncology Group) score of grade 3 or higher, organ dysfunction of grade 2 or higher based on the NCI CTC (National Cancer Institute Common Toxicity Criteria) version 4.0 [22], such as hearing loss and tinnitus and neurologic disorders, hypersensitivity to platinum, pregnancy and lactation, CD4 count less than 200/μl in HIV/AIDS patients. As for renal function, the Panel reached consensus on a cut-off glomerular filtration rate (GFR) value of 50 ml/min/BSA (body surface area) 1.73 m^2 (or a CCR value of <50 ml/min), although a cutoff CCR value of <60 ml/min was generally used to determine ineligibility for high-dose cisplatin-based chemotherapy [23].

Criteria for identifying recipients at moderate to high risk of developing platinum intolerance

Treating the patients falling under these criteria with cisplatin requires extra caution. Some variables previously put in the contraindication group were switched to the high risk group following the panel discussion, such as age, a CCR of 50–60 ml/min, a variety of co-morbidities and social support. Other high risk factors included a performance status score of grade 2, borderline organ function, prior platinum-based therapy including induction chemotherapy, weight loss, nutritional status, and concomitant use of nephrotoxic drugs.

Discussion

Age, co-morbidity and organ dysfunctions appear to be the most important factors that need to be considered in decision making. Regarding special populations at increased risk of toxicity [36], managing elderly patients, together with cognitive function and geriatric syndromes, is a top priority for physicians to handle.

Table 2
Finalized outputs of Group A. Clinical criteria for absolute contraindications to cisplatin.

Listing items (physiological system/ clinical condition)	Rationale	Clinical/laboratory parameters for selection/cut-off	Supporting literature/clinical evidence
Performance status	Poor compliance	ECOG score ⩾3	ECOG performance status scoring [24]
Renal dysfunction	Worsening of toxicity Risk of fluid overload or dehydration Correlating with ototoxicity	CCR <50 ml/min	Real-life clinical practice and literature on cutoff CCR value [23]
Otologic disorders	Permanent hearing impairment affecting quality of life	Medical history: pre-existing hearing loss or tinnitus ⩾ grade 2	Literature on platinum-induced ototoxicity [25]
		Abnormal audiometry within audible frequency (audiometric criteria: threshold shift > 25 dB averaged at 2 contiguous test frequencies or hearing loss but hearing aid or intervention is not indicated)	NCI CTC criteria version 4.0 [22]
Neurologic disorders	Neuropathy	⩾grade 2 (e.g. diabetic neuropathy, peripheral sensory neuropathy, orthostatic hypotension, Lhermitte's sign, seizures, and focal encephalopathy)	Literature on platinum-induced neurotoxicity [22,26]
Known hypersensitivity to platinum based therapy	Unforeseen reactions	Allergic to agents that contain platinum or mannitol: skin rash, flushing, cardiovascular and respiratory complications	Literature on hypersensitivity reactions associated with platinum agents [27]
Pregnancy and lactation	Adversely affecting embryogenesis, increased risk of fetal toxicities	Avoiding pregnancy Breast feeding not recommended	Literature on platinum based chemotherapy and pregnancy [28]
HIV/AIDS	Weakening of immune system	WHO definition: CD4 count <200/μl	WHO clinical staging of HIV/AIDS [29]

Table 3
Finalized outputs of Group B. Clinical criteria for high risk cases.

Listing items (physiological system/clinical condition)	Rationale	Clinical/laboratory parameters for selection/cut-off	Supporting literature/clinical evidence
Performance status	Poor compliance	ECOG score = 2	ECOG performance status scoring [24]
Biological age	No benefit from addition of cisplatin based chemotherapy	>70 years old Geriatric assessment Cognitive function	Evidence from meta-analysis [3,30]
Renal dysfunction	Worsening of toxicity Risk of fluid overload or dehydration	CCR = 50–60 ml/min Doses < 100 mg/m^2 should be considered	Real-life clinical practice and literature on cutoff CCR value [23]
Borderline function of target organs –Otology –Neurology	Worsening of toxicity	NCI CTC criteria for borderline organ function: grade 1 Medical history	Toxicity profile NCI CTC criteria version 4.0 [22]
Dysfunction of other organs	Presence of anemia Hepatic impairment	Marrow, hepatic, and respiratory dysfunction ⩾ grade 2 Child-Pugh score = B	Toxicity profile NCI CTC criteria version 4.0 [22]
Co-morbidities	Increased risk of toxicity due to delayed hepatic metabolism Accelerating ageing of the kidney	Cardiovascular disease including hypertension, unstable cardiac disease, diabetes, and recurrent pulmonary infections	Toxicity profile Literature on influence of hypertension and diabetes on kidney [31,32]
HIV/AIDS or immuno-compromised conditions	Weakening of immune system	Stage III, CD4 count <350/μl according to WHO definition	WHO clinical staging of HIV/AIDS [29]
Previous platinum therapy including induction chemotherapy	Long-term cardio-toxicity, increased risk of cumulative toxicity, poor compliance	>200 mg/m^2 >3 cycles TPF induction therapy	Toxicity/compliance profile TREMPLIN [8], Literature on circulating plasma platinum [21]
Weight loss and nutritional status	Serious and dose-limiting side effect	Involuntary weight loss ⩾ 20%	Literature on influence of weight loss on patient outcomes [33]
Concomitant use of nephrotoxic drugs	Worsening of toxicity, altering pharmacology of cisplatin	Medical history	Literature on how concomitant use of nephrotoxic drugs alter pharmacology of platinum agents [34]
Socioeconomic status/social and home support	Toxicity and compliance	History/clinical No social support, no support at home	Toxicity profile Literature on importance of home and social support [35]

Co-morbidity and organ dysfunctions usually involve renal, auditory, neurologic, cardiovascular, hepatic, and bone marrow disorders. As for functional status, mostly patients with ECOG performance status of ⩾3 are often better served with best supportive care only. We have also factored in HIV/AIDS, polypharmacy, hypersensitivity, pregnancy and lactation, nutritional status, and socioeconomic issues.

Performance status is used to quantify cancer patients' general well-being and activities of daily life, thereby determining whether they can receive chemotherapy or whether dose adjustment is necessary. The lower compliance to chemotherapy and the fear of a higher risk of toxicity are often noted in patients with an ECOG score of 2 or higher. Given the concept of absolute contraindication put forward at the meeting, an ECOG performance status graded as 2 was regarded as a high risk factor, and a grade of 3 or higher as a contraindication.

In some countries in Asia the use of cisplatin is not recommended in patients aged 75 and over. Important with respect to the treatment of patients with LA-SCCHN is the observation in the MACH-NC meta-analysis that no clear benefit of CCRT over RT could be found in patients over 71 years of age [3]. However, it was understood that this observation was not based on biological age but calendar age. Therefore, a more comprehensive and objective assessment of the individual was felt to be more appropriate as a selection procedure than chronological age alone, and failure to do so may lead to suboptimal treatments being chosen with possible inferior outcomes [37]. However, the discussion on the age of patients with LA-SCCHN is relevant not only to the point of co-morbidities but also from the perspective of maintaining the social and holistic impact of the patient's performance after cure of the disease. As noted from demographic studies, HPV positive cases generally belong to the young working-age population, who, in addition to having a favorable prognosis after treatment, also contribute to the familial, societal and national productivity of a nation. Avoiding undue residual toxicities, which may considerably handicap normal functioning capacity, may be valuable in the long term.

Renal dysfunction is critical as the kidney itself is of great importance in physiologic activity, and moreover in case of dysfunction this may lead to increased platinum levels thereby putting patients at a higher risk of other toxicities as well as fluid overload or dehydration. For example, nephrotoxicity was found significantly correlating with the occurrence of ototoxicity ($P = 0.011$) [19]. Assessment for signs and symptoms of fluid volume overload or deficit is also necessary. The debate revolved around the issue of renal dysfunction at this meeting. A compromised renal function is generally defined as a CCR of being lower than 60 ml/min. When kidney function decreases (CCR 40–60 ml/min), it is generally advised to reduce the dose of cisplatin by 50% and when the CCR is less than 40 ml/min cisplatin should be stopped.

To prevent the worsening of ototoxicity it would appear that a CCR of <60 ml/min could be considered a relative contraindication to cisplatin. In some countries (e.g. China), cisplatin is stopped in SCCHN patients with a CCR of <60 ml/min, and carboplatin is used instead for patients with a CCR of 40–60 ml/min. Platinum agents are stopped totally when the CCR is less than 40 ml/min. However, in Hong Kong and Korea 75% cisplatin can still be used for a CCR of 50–60 ml/min. The panel finally reached consensus on a cut-off value of 50 ml/min as an absolute contraindication to cisplatin based therapy to take into account the clinical practice in the real-life setting and give balanced coverage of various opinions. Those with a CCR of 50–60 ml/min should be treated with caution, and doses lower than 100 mg/m^2 should be considered in that

situation. However, the consensus was to aim at achieving a cumulative cisplatin dose of 200 mg/m^2 during RT [38].

Based on the NCI CTC version 4.0 [22], disorders of grade 2 or higher, including hearing impairment, tinnitus and neuropathy, were classified as contraindications. If graded as 1, such disorders were considered as high risk factors. It is clinical practice in China that any adverse effects greater than grade 2 must lead to anticancer chemotherapy discontinuation. Hearing tests are usually not available in routine clinical practice, which necessitates physicians' attention to patients' medical history regarding hearing problems.

On the other hand, a variety of disorders of grade 2 or higher, such as bone marrow, hepatic, and respiratory dysfunction, as well as co-morbidities including cardiovascular disease and diabetes, were allocated to the high risk group.

It should be noted that co-morbidities not only can increase the risk of toxicity, drugs used to treat co-morbidities may also interact with chemotherapeutic drugs, thereby further increasing toxicity. Chronic systemic hypertension and diabetes mellitus can accelerate ageing of the kidney, thus increasing the sensitivity of the kidney to the toxic effects of cisplatin.

Toxicities resulting from bone marrow dysfunction must be corrected in patients with cancer. Anemia is usually present because of the disease or its treatment and, if left uncorrected, it can not only alter drug activity and increase toxicity but also represent a risk factor for decreased distribution of water-soluble drugs, cardiovascular disease, congestive heart failure, coronary death and possibly dementia. In addition to the NCI CTC version 4.0, the Child-Pugh score is often used to assess the prognosis of chronic liver disease. Hepatic impairment described as Child-Pugh grade B may increase the risk of developing cisplatin induced toxicity.

In patients with head and neck cancer undergoing CCRT, the early nutritional management can reduce weight loss and improve outcome. Both nutritional deficiency and weight loss (involuntary weight loss $\geqslant$20%) represent high risk to platinum based therapy. Concomitant use of nephrotoxic drugs, another risk factor, can affect renal blood flow and renal tubular properties, and may alter the pharmacology of platinum agents.

Prior platinum, including prior induction chemotherapy, is regarded as a risk factor, not only with respect to tolerance and compliance, but also to long-term cardiovascular toxicity. It can be expected that giving cisplatin based induction chemotherapy before cisplatin based CCRT is leading to more toxicity because of the subsequently increased cumulative dose of cisplatin. As mentioned earlier, this approach is not recommended as a standard form of treatment in LA-SCCHN. However, induction chemotherapy followed by different forms of locoregional treatment is getting major attention in clinical trial settings, e.g. in HPV positive oropharynx cancer [39].

People with HIV/AIDS have had a weakened immune system, before they even start cancer treatment. Chemotherapy can further weaken the immune system, and potentially might have a further negative effect on the outcome. Some aspects of treatment may need to be adjusted in people with HIV/AIDS. Based on the WHO definition, we placed those with a CD4 count of <350/μl into the high risk group, and agreed that cisplatin was contraindicated in those with a CD4 count of <200/μl.

Home and social support is critical in providing patients with valuable sources for hope in their care. Healthcare providers can develop proactive strategies to shelter patients from the negative aspects of cancer and chemotherapy. Lack of home and social support may therefore pose a high risk.

Also included into the contraindications were known hypersensitivity to platinum based therapy and pregnancy and lactation. The former may lead to cardiovascular and respiratory complications that can prove fatal. As for the latter, exposure to chemotherapy after the first trimester of pregnancy is associated with increased risk of fetal toxicities. Because of the relatively long half-life of cisplatin, discontinuation of breastfeeding is usually recommended.

In this paper, the recommendations for the criteria were largely developed by synthesizing expert opinions from the Asia Pacific Region (e.g. cutoff values for age, CCR, ECOG score, CD4 count) and mechanism based reasoning (e.g. circulating plasma platinum, acceleration in kidney aging in diabetics). Although the level of evidence cannot be graded as high enough, these recommendations are still based around literature; and moreover, such consensus statements may indicate possibilities for future research.

As mentioned earlier, methods to reduce or avoid the toxicity of cisplatin-based CCRT in SCCHN include better radiotherapy targeting [CT (computed tomography) – MRI (magnetic resonance imaging) – PET (Positron emission tomography) and IGRT (image guided radiotherapy)], new radiotherapy techniques [IMRT (intensity modulated radiotherapy) and SW-IMRT (swallowing sparing IMRT), stereotactic radiotherapy, and IMPT (intensity modulated proton therapy)], and alternatives to cisplatin, such as other cytotoxics (carboplatin, taxanes, low-dose gemcitabine) and biological agents (cetuximab).

Carboplatin is frequently used to replace cisplatin because of its similar mode of action, but lower rates of ototoxicity, nephrotoxicity, neurotoxicity and emesis [40]. Carboplatin has also the advantage of being primarily eliminated by excretion with the urine, and therefore it can be better dosed based on glomerular filtration rate (GFR). As such, carboplatin can also be used in a setting of diminished kidney function. Dosing based on the GFR (in practice the CCR is used for this) according to the Calvert formula [total carboplatin dose (mg) = (target AUC) $\times$ (GFR + 25)] is common practice in solid tumor treatment, and the method results in a better dosage for individual patients than the BSA based dosing strategy [41]. However, elderly patients and those with a poor performance status and history of extensive pretreatment still have a higher risk of toxicity. Despite the fact that large randomized trials comparing carboplatin and cisplatin in the CCRT setting are lacking, carboplatin is frequently used in routine clinical practice when cisplatin is not tolerated or contraindicated. It should be noted that the use of carboplatin plus RT did not result in overall survival improvement versus RT alone in the MACH-NC meta-analysis [3]. Despite the fact that more contemporary studies suggest it might be a reasonable option when cisplatin is contraindicated, adequate trials supporting this notion are urgently needed.

On the other hand, cetuximab is a synergistic chemosensitizer and radiosensitizer, as observed from preclinical and several clinical studies [7,42]. Treatment adherence of >90% with cetuximab plus RT seems better than that with cisplatin-based CCRT, with no impact on quality of life as compared with RT alone [7,43]. However, as mentioned earlier, there has been no definitive answer as to whether cetuximab can replace cisplatin in CCRT because no direct head-to-head comparison of chemoradiation and bioradiation in phase III has been reported. Studies in that direction are under way.

Conclusion

Based on literature review and panel discussion, the Expert Panel succeeded in developing a set of clinical criteria for defining platinum unsuitable patient populations with head and neck cancer, which could be applied to clinical practice. In case of platinum ineligibility, replacing cisplatin with other (less toxic) cytotoxic agents or cetuximab may be taken into consideration. Trials are under way to generate stronger supporting data.

Conflict of interest statement

The authors are fully responsible for the content of this manuscript, which reflects the views and opinions of the authors only. Synergy Global Partners provided logistic support in the organization of the meeting and editorial assistance; medical writing assistance was provided by Dr. Feng Xue. All authors received an honorarium from Merck Serono.

Dr. Feng Xue is a freelance medical writer, and in that capacity has provided services for a number of pharmaceutical companies and medical communications agencies. He has no specific conflicts of interest in relation to this publication.

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References

[1] WHO International Agency for Research on Cancer: GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. <http://globocan.iarc.fr/> [accessed February 2015].
[2] National Cancer Institute: SEER cancer statistics review 1975–1998. Bethesda (MD).
[3] Pignon JP, leMaitre A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.
[4] Gregoire V et al. Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21(suppl 5):v184–6.
[5] National Comprehensive Cancer Network: NCCN Guidelines v2; 2014. <http://www.nccn.org/professionals/physician_gls/f_guidelines_nojava.asp#site> [accessed October 2014].
[6] Machtay M et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26:3582–9.
[7] Bonner JA et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–78.
[8] Lefebvre J, Pointreau Y, Rolland F, et al. Sequential chemoradiotherapy (SCRT) for larynx preservation. J Clin Oncol 2012;30. 360s (suppl 15; abstr 5501).
[9] Petrelli F et al. Concomitant platinum-based chemotherapy or cetuximab with radiotherapy for locally advanced head and neck cancer: a systematic review and meta-analysis of published studies. Oral Oncol 2014;50(11):1041–8.
[10] Psyrri A et al. Human papillomavirus-related head and neck tumors: clinical and research implication. Curr Opin Oncol 2009;21(3):201–5.
[11] Ang KK et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.
[12] Posner M et al. Survival and human papillomavirus in oropharynx cancer in TAX324: a subset analysis from an international phase III trial. Ann Oncol 2011;22:1071–7.
[13] O'Sullivan B et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol 2013;31(5):543–50.
[14] National Institute for Health and Care Excellence: NICE head and neck cancer guidelines 2014. <https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/head-and-neck-cancers> [accessed October 2014].
[15] Alderden RA, Hall MD, Hambley TW. The discovery and development of cisplatin. J Chem Ed 2006;83(5). 728–724.
[16] Vermorken JB, van der Vijgh WJ, Klein I, Hart AA, Gall HE, Pinedo HM. Pharmacokinetics of free and total platinum species after short-term infusion of cisplatin. Cancer Treat Rep 1984;68:505–13.
[17] Vermorken JB et al. Pharmacokinetics of free and total platinum species following rapid and prolonged infusions of cisplatin. Clin Pharmacol Ther 1986;39:136–44.
[18] Vermorken JB et al. Pharmacokinetics of free platinum species following rapid, 3-hour and 24-hour infusions of cis-diamminedichloroplatinum (II) and its therapeutic implications. Eur J Cancer Clin Oncol 1982;11:1069–74.
[19] Vermorken JB, Kapteijn TS, Hart AAM, Pinedo HM. Ototoxicity of cis-diamminedichloroplatinum (II): influence of dose, schedule and mode of administration. Eur J Cancer Clin Oncol 1983;19:53–8.
[20] Strumberg. D et al. Evaluation of long-term toxicity in patients after cisplatin-based chemotherapy for non-seminomatous testicular cancer. Ann Oncol 2002;13(2):229–36.
[21] Gietema JA et al. Circulating plasma platinum more than 10 years after cisplatin treatment for testicular cancer. Lancet 2000;355:1075–6.
[22] National Cancer Institute: NCI CTCAE criteria version 4.0. <http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf> [accessed October 2014].
[23] Dash A et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer 2006;107(3):506–13.
[24] Eastern Cooperative Oncology Group: ECOG performance status. <http://www.ecog.org/general/perf_stat.html> [accessed September 2014].
[25] Langer T et al. Understanding platinum-induced ototoxicity. Trends Pharmacol Sci 2013;34(8):458–69.
[26] McWhinney SR et al. Platinum neurotoxicity pharmacogenetics. Mol Cancer Ther 2009;8(1):10–6.
[27] Makrilia N et al. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. Metal Drugs 2010. http://dx.doi.org/10.1155/2010/207084 207084.
[28] Society of Obstetricians and Gynecologists of Canada: Cancer chemotherapy and pregnancy. J Obstet Gynaecol Can 2013; 35(3): 263–78.
[29] World Health Organization: Interim WHO clinical staging of HIV/AIDS. <http://www.who.int/hiv/pub/guidelines/clinicalstaging.pdf> [accessed November 2014].
[30] Argiris A, Li Y, Murphy BA, Langer CJ, Forastiere AA. Outcome of elderly patients with recurrent or metastatic head and neck cancer treated with cisplatin-based chemotherapy. J Clin Oncol 2004;22:262–8.
[31] Hill GS. Hypertensive nephrosclerosis. Curr Opin Nephrol Hypertens 2008;17:266–70.
[32] Perkins BA, Krolewski AS. Early nephropathy in type 1 diabetes: the importance of early renal function decline. Curr Opin Nephrol Hypertens 2009;18:233–40.
[33] Capuano G et al. Influence of weight loss on outcomes in patients with head and neck cancer undergoing concomitant chemoradiotherapy. Head Neck 2008;30(4):503–8.
[34] Kimmick GG et al. Cancer chemotherapy in older adults. Drugs Ageing 1997;10(1):34–49.
[35] Phister JE et al. Problems in the use of anticancer drugs in the elderly. Drugs 1989;37:551–6.
[36] Haigentz Jr M et al. When is chemotherapy in head and neck squamous cell carcinoma not indicated? Eur Arch Otorhinolaryngol 2014. http://dx.doi.org/10.1007/s00405-014-2894-9.
[37] Camilon PR, Stokes WA, Nguyen SA, et al. Are the elderly with oropharyngeal carcinoma undertreated? Laryngoscope 2014;124:2057–63.
[38] Nguyen-Tan PF et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol 2014;32(34):3858–67.
[39] Marur S et al. ECOG 1308: a phase II trial of induction chemotherapy followed by cetuximab with low dose versus standard dose IMRT in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx (OP). J Clin Oncol 2012;30(suppl. 15). ASCO Annual Meeting abstract 5566.
[40] Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: an analysis of the literature. Annals Oncol 1998;9:13–21.
[41] Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989;7:1748–56.
[42] Vermorken JB et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116–27.
[43] Curran D et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol 2007;25:2191–7.