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REWIEW

Optimal Dose of Cisplatin (CDDP) Given Concurrently with Radiotherapy (RT) in Locally Advanced Squamous Cell Head and Neck Cancer (SQC HNC)

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SUMMARY

Meta-analyses of chemotherapy in Head and Neck Cancer (MAC-HNC) showed that adding chemotherapy (CHT) to locoregional treatment improves the treatment outcome. However, it was observed only with concurrent administration of radiotherapy (RT) and CHT. Among many drugs used in this setting, cisplatin (CDDP) has most consistently been used as a single-agent with radical RT. The two most common administrations of CDDP included 100 mg/sqm every three weeks and 40 mg/sqm weekly, both during the course of RT. While a direct comparison of the two modes of CDDP administration in the definitive treatment of locally advanced squamous cell (SQC) HNC is basically lacking, recent summary brought somewhat conflicting results. Questions largely unexplored is the total CDDP dose deemed necessary when administered concurrently with radical RT. Subset analyses from various prospective randomized trials and meta-analyses seem to indicate that one may not need a total CDDP dose of significantly higher than 200 mg/sqm if at all higher than that, irrespective of the type of RT administered and seemingly unnecessary in HPV+ oropharyngeal cancer patients. Due to presumably lower but still effective threshold level of total CDDP given with RT may depend on other factors, such as frequency of CDDP administration or RT fractionation pattern and be closely interrelated with anticipated toxicity, researchers continue with their quest to find optimal approach in this setting. Large clinical trials should detect small differences between treatment options in an era when "old" but effective drugs still dominate the research arena of SQC HNC.

Keywords: Cisplatin; chemotherapy; head and neck cancer; radiotherapy.

Introduction

Locally advanced squamous cell head and neck cancer (SQC HNC) represent a significant therapeutic challenge for head and neck oncologists. While all three treatment modalities, surgery, radiation therapy (RT) and chemotherapy (CHT) were used in the past several decades, meta-analyses of chemotherapy in HNC (MAC-HNC) using individual patient data (IPD) [1,2] showed that adding CHT to locoregional treatment improves the treatment outcome. While induction and adjuvant CHT did not offer a significant advantage, it was observed only with concurrent administration of RT and CHT.

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Among many drugs used in this setting, cisplatin (CDDP) has most consistently been used as a single-agent with radical RT (mostly 70 Gy in 35 daily fractions over seven weeks). It was administered as three cycles of 100mg/m^2 on days 1, 22 and 43 of the RT course. This specific administration, however, leads to a significant toxicity and frequent dose omissions or reduction and frequent treatment interruptions. Therefore, researchers attempted to offer an alternative via altered administration of CDDP, using mostly 40 mg/m^2 given weekly for seven weeks. This was based on the assumption that it would lead to lesser toxicity while, at the same time, offer better (more prolonged) radiosensitization due to a more frequent CDDP administration. While a direct comparison of the two modes of CDDP administration in the definitive treatment of locally advanced SQC HNC is basically lacking, a recent summary of existing meta-analyses that attempted to solve this issue disclosed somewhat conflicting results.[3] One of the questions that also remains largely unexplored is the total CDDP dose that may seem as necessary to reach when administered concurrently with radical RT irrespective of the mode of CDDP administration (weekly or three weekly or daily) or RT fractionation (conventional-CF, hypofractionated-Hfx or accelerated-Acc).

Total dose of CDDP administered with concurrent RT

In addition to data from trials that showed that only 60-80% of the patients were able to receive all three cycles of 100 mg/m^2 of CDDP, some studies indicated that CDDP could be administered more frequently with reduced toxicity and good both local control and survival. Studies of SAKK [4] (total, 200 mg/sqm) and Jeremic et al.[5,6] (total, 210 mg/m^2) showed that one might perhaps not need 300 mg/sqm total CDDP dose for good results. As discussed by Ang [7], perhaps again, a cumulative dose of CDDP of approximately 200 mg/m^2, might need not be significantly surpassed, if at all, if one expected a beneficial antitumor effect. The results of two meta-analyses seem to add to this suggestion. Analysis carried out regarding the CHT in MAC-HNC [1,2] showed that single-agent cisplatin (CDDP) given with radical RT might be preferred treatment option, with an interesting observation that the single negative concurrent RT/CDDP study was the one where total cumulative CDDP dose was 140 mg/m^2.[8] Italian literature-based meta-analysis of concurrent RT/CDDP in SQC HNC, although published only in an abstract form [9], did not observe reduced risk of death between total cumulative doses of CDDP of 300 mg/m^2 and <300 mg/m^2, both given with 5- fluorouracil (5-FU), when RT/CDDP/5-FU was compared to RT alone. Importantly, however, when CDDP was administered without 5-FU, there was a significant difference in death risks between total cumulative CDDP dose of 200–225 mg/m^2 (HR, 0.68) and total cumulative dose of <150 mg/mV; (HR, 1.04). Intrigued by these discussions and subset analyses, HNC researchers readily responded by embarking on further studies aiming to additionally enlighten this issue.

An international collaborative group [10] undertook a systematic review to evaluate evidence on the CDDP dose-response when given concurrently with RT in locally advanced, nonmetastatic SQC HNC. They have used an indirect approach that compared the survival of RT alone versus RT and different CDDP dose intensities. There were 11 randomized trials (of which eight were definitive treatments) and seven non-randomized studies. While no significant relationship was observed between the cumulative CDDP dose and the survival advantage on a linear regression done with all randomized trials when the analysis was limited to trials with definitive RT (n=6), superior OS was noted for higher total cumulative CDDP doses, the relationship is linear. There was a 2.2% (95% CI, 0.4%-4%) absolute benefit in OS favoring RT/CDDP over RT-only arm observed for every 10 mg increase in the cumulative CDDP dose. In the range of doses of CDDP that existed in those studies (140 mg/m^2 to 270 mg/m^2), the model was statistically significant (p=0.027). Unfortunately, due to a small available data points, other endpoints could not be meaningfully evaluated, leaving, therefore, an unanswered question of whether improvement in any of these endpoints (e.g., locoregional tumor control) may have contributed an improvement in OS for higher total cumulative CDDP doses.

Similarly, Carlsson et al.[11] reviewed the literature with the aim of comparing high-dose (3 weekly 100 mg/m^2) to low dose CDDP given concurrently with radical RT, the latter including both weekly and daily CDDP administration. There were six prospective and seven retrospective studies. The median 3-year OS was 68% for high-dose CDDP and 61% in low dose CDDP. The 3-year locoregional failures were 21% versus 28%, while distant metastases were 13% versus 14.5% for the two CDDP administrations, respectively. The cumulative dose of CDDP was reported in five out of eight studies using high-dose CDDP and in three out of six of those using low-dose CDDP. Of these eight trials, the median cumulative CDDP dose was available in three trials only, while five trials lacked such data. Overall, a median of 86% versus 79% of patients received a cumulative CDDP dose of ≥200 mg/m^2 in high dose versus low dose regimens, respectively. Due

to the inability of authors to perform formal statistical comparisons, their findings remained, unfortunately, mainly descriptive.

It is also important to put these data and observations into the context of existing and increasingly used altered fractionated RT regimens, as well as to emphasize the importance of increasing scientific focus after the emergence of HPV+ HNC, in particular, oropharyngeal cancer (OPC) as a separate entity. Altered fractionated RT regimens have been practiced for decades and have shown both in prospective randomized trials [12] and meta-analysis [13] to have an advantage over conventionally fractionated RT. Although it was shown that this intensification of the RT approach is usually accompanied by an increase in toxicity, HNC researchers, nevertheless, attempted to combine it with CHT, CDDP being given either alone or in combination with 5FU. In one such study, RTOG0129, three cycles of CDDP were given conventionally with fractionated RT and were compared to an accelerated RT regimen with concurrent two cycles of CDDP. Both initial report [14] (OS; hazard ratio, HR, 0.90; 95% CI, 0.72 to 1.13) and its long term update [15] (OS, HR, 0.96; 95% CI, 0.79 to 1.18; p=0.37; 8-year survival, 48% vs. 48%), PFS (HR, 1.02; 95% CI, 0.84 to 1.24; p=0.52; 8-year estimate, 42% vs. 41%), LRF (HR, 1.08; 95% CI, 0.84 to 1.38; p=0.78; 8-year estimate, 37% vs. 39%), or DM (HR, 0.83; 95% CI, 0.56 to 1.24; p=0.16; 8-year estimate, 15% vs 13%) showed any difference favoring higher dose CDDP and intensified RT. The authors hypothesized that the lack of benefit of accelerated RT could be a result of the total of three cycles of CDDP which, still managed to compensate for presumably higher tumor clonogen repopulation presumably happening during the prolonged fractionated RT course (seven weeks). In other words, one week, which was "saved" in accelerated RT, seemed to have had an equal effect as approximately one (the third) cycle of CDDP. Indirectly supporting these data are the data from GORTEC 99-02 (The Groupe d'Oncologie Radiothérapie Tête et Cou), a three-arm randomized phase III trial of RT with or without CHT in locally advanced SQC HNC.[16] Two arms consisted of RT (CF or Acc), and concurrent CDDP, the former being given with three cycles, the latter with two cycles. Similarly to RTOG0129 [14,15], no difference was found in outcomes between the two RT-CHT arms. However, interesting data from a recent meta-analysis compared altered fractionated regimens with two cycles of concurrent CDDP (100 mg/sqm) given with a 3-4 week split with weekly low dose CDDP regimens (<50 mg/sqm for >4 doses).[17] Despite similar overall and complete response rates, altered fractionated regimens, and two cycles of high dose CDDP achieved superior overall survival (p=0.0185). Interestingly, planned high dose CDDP had been delivered with better compliance than low-dose weekly CDDP (95% vs. 71%, p=0.0353). Furthermore, it led to significantly less severe acute and late toxicity, including 30-day mortality. Authors concluded that even with altered fractionated regimens, almost all patients have been able to receive planned 200 mg/m^2.

While HPV+ HNC had become one of the major focuses of clinical research in HNC/OPC, identification of risk groups led to an attempt towards treatment de-intensification. Initial results showed the superiority of RT/CDDP over RT/cetuximab in two recent prospective randomized trials.[18,19] In both studies, CDDP 100 mg/sqm was used, and no subset analysis regarding planned versus delivered dose and relationship with outcome was provided. However, Spreafico et al.[20] retrospectively analyzed all patients with OPC, carcinoma of the unknown primary and laryngo-hypopharyngeal region from two institutions irrespective of their HPV status treated with RT and single-agent CDDP and directly compared two distinct HPV status groups of patients. In patients with HPV- cancers, 3-year OS for the patients who received total CDDP dose <200, =200, and >200 mg/m^2 were 52%, 60%, and 72%, respectively (p=0.001) while corresponding figures for HPV+ cancer patients were 91%, 90%, and 91%, respectively (p=0.30). In HPV-cancer patients, the total dose of CDDP >200 mg/m^2 was independent prognostic factor for improved survival (HR, 0.5, 95% CI: 0.3-0.7, p<0.001). Contrary to this, no such observation was made in HPV+ patients (HR 0.6, 95% CI: 0.4-1.1, p=0.104). However, a subset analysis of patients with HPV+ status showed that there was a strong trend favoring OS in the T4 or N3 high-risk group when a total doe of CDDP >200 mg/m^2 was given (HR 0.5, 95% CI: 0.2-1.1, p=0.07). These results indicated that for the present times, a total CDDP dose of >200mg/sqm might not be important in all HPV+ patients, rather in patients who are deemed the high risk for locoregional and/or distant failure. On the other side, HPV- patients seem to remain dependent on the total CDDP dose due to significantly superior outcomes with doses of >200 mg/m^2 in both univariate and multivariate analysis.

Conclusion

While high-level evidence from prospective randomized trials and meta-analysis directly comparing various total doses of CDDP (e.g., <200 vs. >200 mg/m^2) are unfortunately lacking, researchers and clinicians are more prone to attempt to achieve a total CDDP at

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least 200 mg/m^2 when administered concurrently with radical RT, either CF or altered RT in the definitive management of locally advanced SQC HNC. Having in mind that presumably lower but still effective threshold level of total CDDP given with RT may depend on other factors, such as frequency of CDDP administration or RT fractionation pattern, and be closely interrelated with anticipated toxicity, researchers continue with their quest to find optimal approach in this setting. Prospective and powerful clinical trials should detect small differences between treatment options in an era when "old" but efficient drug CDDP still dominates the research arena of SQC HNC.

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