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REWIEW

Optimal Administration Frequency of Cisplatin Concurrently With Radical Radiotherapy in the Definitive Treatment of Locally Advanced, Inoperable Squamous Cell Cancer of the Head and Neck. Still Obscured by Clouds?

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SUMMARY

Here we present a summary of existing evidence from meta-analyses and systematic reviews in the setting of locally advanced, inoperable squamous cell cancer of the head and neck, treated with radical radiotherapy and concurrent cisplatin therapy either weekly or every 3 weeks. Taken together, the data seem to indicate that there is no difference in major outcomes, including toxicity. However, caution in the interpretation of the data should be exercised due to poor quality of original studies, none of which was a prospective randomized phase III trial. Practicing clinicians should continue using their best judgment about the most appropriate treatment option in this setting, taking into account both the existing evidence and also various patient and tumor characteristics.

Keywords: Cisplatin; head and neck cancer; locally advanced disease; radiotherapy.

Introduction

Optimal treatment of patients with locally advanced squamous cell head and neck cancer (LA SCC H&N) is one of the major challenges in H&N oncology. While selected patients are treated with surgery and postoperative radio (chemo) therapy (RT-CHT), the vast majority of patients are deemed inoperable from the start. In such cases, combined RT-CHT has been practiced for decades. An extensive body of data within meta-analyses based on individual patient data enabled the investigation of the optimal sequence administration of the two treatment modalities. It was shown that neither induction CHT followed by RT or RT followed by adjuvant CHT offered any benefit over locoregional (in this case exclusive) RT. The only benefit was seen with concurrent RT-CHT, with the following magnitude: 6.5% absolute 5-year survival benefit with the hazard ratio of 0.81 and 95% confidence intervals (CI) 0.74–0.86 ($p<0.0001$).[1] Importantly, the same benefit was observed irrespectively of the type of RT used (conventional or altered fractionated) or whether postoperative RT had been used. Regarding the CHT issues, there were no differences between the single-agent and mufti-agent CHT, although in the single-agent group of trials, platinum-based regimens were found to be more effective than any other single-agent regimen. Unfortunately, this meta-analysis did not provide solid data on superiority of the type of the administration and the single or total dose of any of the used single-agent platinum regimens concurrent with radical RT.

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The issue of optimal administration of RT and CDDP in the definitive treatment remained unsolved, despite the fact that doses of 100 mg/m^2 applied every 3 weeks were both suggested and largely practiced [2,3] in the past three decades. In recent years, however, we have seen the introduction of a weekly administration of CDDP, mostly at a dose of 40 mg/m^2, expecting to lead to less toxicity and potentially better (if not the same) radiosensitization, ultimately leading to a better therapeutic ratio. Unfortunately, high-quality and multiple prospective randomized trials (RCTs) investigating the issue of concurrent use of weekly vs. CDDP and RT applied every 3 weeks are strikingly lacking. This may be one the reasons why several meta-analyses and systematic reviews had been performed in recent years.

The last few years witnessed several attempts to address the issue of optimal administration of CDDP concurrently with radical RT. There are currently four meta-analyses/systematic reviews (Table 1) that should have provided a detailed, both quantitative and qualitative, synthesis of the existing data.[4-7] The data from the most recent study by Sturz et al. from 2019 [8] are the same as ones published originally in 2017.[5] Different time periods focused upon in these meta-analyses naturally resulted in a different number and type of studies included (main and separate analysis), and consequentially a different patient number, unfortunately not always specified. Additionally, the level of evidence stemming from included studies greatly diverged regarding various pretreatment (e.g.,., diagnostic and staging criteria used in different time periods; inclusion of NPC) and treatment (e.g.,., accelerated RT; total CDDP doses only when >180 mg/m^2; a weekly dose ranging from 20 mg/m^2 to 50 mg/m^2). In addition, inconsistent reporting was one of the main concerns. One may, therefore, not be surprised to observe a great diversity between these four meta-analyses, none of which provided individual patient data.

In spite of these shortcomings, it is remarkable to observe that there is no significant difference in not only OS, but LRFS, PFS, and RR as well. Regarding toxicity, while Guan et al.[4] and Mohamed et al.[7] found no difference in any of documented toxicities, Jacinto et al.[6] found Grade >3 mucositis significantly more frequent in weekly CDDP, but only in a single RCT (using postoperative RT-CHT), while there was no difference in six retrospective studies using concurrent RT-CHT alone. In Sturz et al.[5], the administration of CDDP every 3 weeks led to significantly more leucopenia, neutropenia, N&V and nephrotoxicity, with no difference in incidence rates of stomatitis and mucositis. The only study that found the 3-weekly regimen less toxic was that of Guan et al.[4], but only when high-grade mucositis in non-NPC treated with RT-CHT alone was considered separately from those of NPC cases. Taken all the available data from these four meta-analyses, and as an attempted summary, the existing evidence likely points toward similarity between the two CDDP regimens in this setting.

While proponents and practitioners of weekly CDDP may instantly jump at our conclusions as additional justification supporting their view, we would call for a cautious interpretation of the existing data. The lack of high-quality prospective phase III RCT are not only badly needed, but meta-analyses rarely can control for the lack of it when using the data from retrospective studies with their inherent biases and frequently poor quality which never, therefore, provide relief to that painful situation. Frequently we do not get even a hint to many issues we believe are of paramount importance for the future optimization of RT-CHT. They include, but are not limited to

1. Demystification of the nature and mechanisms of radiosensitization of weekly vs. 3-weekly CDDP given concurrently with radical RT (standard or altered fractionation) from the standpoint of both pharmacokinetics and pharmacodynamics, that is, which of the two regimen produces more effective radiosensitization [9,10]
2. Optimal total cumulative dose of CDDP given concurrently with radical RT [11]
3. Taking into account the promising results of using extreme CDDP fractionation, that is, daily low-dose CDDP given with either radical standard [12] or hyperfractionated RT [13], including a possibility of replacing CDDP with carboplatin (CBDCA) [11] at least when CDDP administration is prohibited
4. Observed difference between HPV– and HPV+ oropharyngeal patients (not subject of any of these meta-analyses), an information supporting the pathway to de-escalation of the treatment, which may be both feasible and effective [14];
5. Magnitude of the effect of impact of the p16 status due to the indication p16+ OPC patients may achieve superior results when compared to p16– patients [15]
6. A better definition of the place and role of altered fractionated regimens and novel RT techniques [16]

We are aware that these concerns are floating around the world and that researchers are trying to actively contribute to this field by producing high-quality prospective RCTs, which remain our best tool to obtain high-level evidence to be used in medicine. We are, however, are also certain that daily clinical practices would largely be governed by each patient coming to the treating physician, bearing its own mix of patient and tumor characteristics of the unique disease influencing the final decision about preferred regimen. Again, they include, but are not limited to the following:

Table 1 Characteristics of meta-analyses

Author	Study period	Study (n)	Pts (n)	OS (2 yr)	OS (3 yr)	OS (5 yr)	Other endpoints	Side effects	Comments
Guan (2016)	2006-2014	10	779	HR, 0.5; p=0.85	HR, 1.12; p=0.85	HR, 1.79; p=0.06	LRFS (1 yr): HR, 1.26; p=0.65 LRFS (2yr): HR, 1.14; p=0.74	• Grade >3 neutropenia: RR, 0.85; p=0.57 • Grade >3 thrombocytoopenia: RR, 1.13; p=0.81 • Grade >3 N&V: RR, 0.59; p=0.06 • Grade >3 dermatitis: HR, 1.23; p=0.29 • No difference in Grade >3 mucositis (all sites)	• 3 studies included NPC • Non-NPCvs NPC studies – n.s. • Grade >3 mucositis in non-NPC more frequent in weekly CDDP RR, 1.72; p=0.01 • Grade 3 mucositis in NPC RR, 0.65; p=0.29 • Grade >3 dermatitis in non-NCP similar between weekly and 3 weekly CDDP
Sturz (2017) (2019)	1981-2013	39	n.a.	61% vs 61%	53% vs 52%	41% vs 39%	OR rates: 89% vs 80%; p=0.15 CR rates: 58% vs 60%; p=0.75	• Grade >3 Leucopenia: 1% vs 19%; p=0.0083 • Grade >3 neutropenia: 5% vs 18%; p=0.0024 • Grade >3 N&V: 3% vs 16%; p<0.0001 • Grade >3 nephrotoxicity: 1% vs 5%; p=0.0099 • Grade >3 mucositis- n.s. • Grade >3 stomatitis – n.s.	• More oropharyngeal cases in three weekly CDDP
Jacinto (2017)	2000-2016	7	n.s.	RCT data: 71.6% vs 79.3% (p=0.978)	n.a.	Retrospective data: HR, 0.88	RCT data: 1yr LRRFS: 60% vs 71.1%; p=0.806 Retrospective data: 5yr PFS: HR, 0.84	• RCT data Grade >3 mucositis: 75% vs 38.5%, p=0.012 • Retrospective data–Grade >3 nephrotoxicity: RR, 0.66 • Grade >3 mucositis: RR, 0.92 • Grade >3 dermatitis: RR, 0.61	• 1 RCT and 6 retrospective studies • RCT was postoperative RT-CHT
Mohamed (2019)	1970-2015	39	3668	74% vs 67% (p=0.67)	n.a.	48% vs 51% (p=0.6)	OR: 89% vs 72% (p=0.14) LRC: 58% vs 61% (p=0.7) PFS (2yr): 69% vs 62% (p=0.9)	• Hematologic, intestinal, neurologic and renal toxicity: 36% vs 40% (p=0.37) • Mucositis: n.s. (p=0.73)	• Weekly CDDP studies (n=18) • 3 weekly CDDP studies (n=21) • Trials with NPC-only excluded • Postoperative trials excluded • Todal CDDP dose of >180 mg/sqm mandatory

OS: Overall survival; OR: Overall response; CR: Complete response; PFS: Progression free survival; LRFS: Local recurrence free survival; LRRFS: Locoregional recurrence free survival; NPC: Nasopharyngeal cancer; CDDP: Cisplatin; G: Grade; n.s.: Not specified; n.a.: Not available; N&V: Nausea and vomiting; RCT: Randomized clinical trial; HR: Hazard ratio; RR: Risk ratio; RT: Radiotherapy; CHT: Chemotherapy

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1. Elderly and/or frail patients, alcohol and/or tobacco consumers, and those with impaired kidney function will likely be advised for weekly CDDP administration.
2. Individuals with more advanced (higher) T and/or N tumors will likely continue to be advised for the CDDP administration every 3 weeks.

Hence, various medical and non-medical factors may govern the final decision about the best applicability of one of the two regimens. Involved physician's clinical expertise; however, remains crucial, and hopefully, still, based on the highest level of evidence that exists.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors declared no conflicts of interest.

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