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Review

Altered fractionation radiotherapy combined with concurrent low-dose or high-dose cisplatin in head and neck cancer: A systematic review of literature and meta-analysis

Petr Szturz[a,b,*], Kristien Wouters[c,d], Naomi Kiyota[e], Makoto Tahara[f], Kumar Prabhash[g], Vanita Noronha[g], David Adelstein[h], Jan B. Vermorken[d,i]

[a] Department of Internal Medicine, Hematology, and Oncology, University Hospital Brno, Brno, Czech Republic
[b] School of Medicine, Masaryk University, Brno, Czech Republic
[c] Scientific Coordination and Biostatistics, Antwerp University Hospital, Edegem, Belgium
[d] Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[e] Kobe University Hospital Cancer Center, Kobe, Hyogo, Japan
[f] Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Chiba, Japan
[g] Department of Medical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India
[h] Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, United States
[i] Department of Medical Oncology, Antwerp University Hospital, Edegem, Belgium

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ABSTRACT

Objectives: Altered fractionation radiotherapy and concomitant chemoradiotherapy represent commonly used intensification strategies in the management of locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). This meta-analysis compares compliance, safety, and efficacy between two single-agent cisplatin schedules given concurrently with altered fractionation radiotherapy.

Methods: We systematically searched for prospective trials of patients with LA-SCCHN who received post-operative or definitive altered fractionation concurrent chemoradiotherapy. High-dose cisplatin once every three to four weeks (100 mg/m^2, 2 doses) was compared with a weekly low-dose protocol ($\leq$50 mg/m^2, $\geq$4 doses). The primary outcome was overall survival. The secondary endpoints comprised treatment adherence, acute and late toxicities, and objective response rate.

Results: Twelve studies with 1373 patients treated with definitive chemoradiotherapy were included. Compared to the weekly low-dose cisplatin regimen, the three- to four-weekly high-dose cisplatin regimen improved overall survival (p = .0185), was more compliant with respect to receiving all planned cycles of cisplatin (71% versus 95%, p = .0353), and demonstrated less complications in terms of severe (grade 3—4) acute mucositis and/or stomatitis (75% versus 40%, p = .0202) and constipation (8% versus 1%, p = .0066), toxic deaths (4%, versus 1%, p = .0168), 30-day mortality (8% versus 3%, p = .0154), and severe late subcutaneous fibrosis (21% versus 2%, p < .0001). Overall and complete response rates were similar between both chemotherapy schedules.

Conclusion: In chemoradiotherapy incorporating altered fractionation, two cycles of high-dose cisplatin with a three to four week interval are superior to weekly low-dose schedules. Further studies should identify those who might derive the greatest benefit from this intensified approach.

Introduction

Improving patient outcomes, as the ultimate goal in oncology, greatly depends on concentrated efforts to promote public health programs, overcome challenges in diagnosis and disease management, and expand health care availability. In squamous cell carcinoma of the head and neck (SCCHN), the Surveillance, Epidemiology, and End Results (SEER) database revealed a substantial enhancement of the 5-year overall survival rate from 54.7% in 1990s to 65.9% in 2000s, particularly in patients with tongue (including base of tongue) and tonsil

Abbreviations: SCCHN, squamous cell carcinoma of the head and neck; SEER, Surveillance, Epidemiology, and End Results; HPV, human papillomavirus; LA, locoregionally advanced; Gy, gray; RTOG, Intergroup Radiation Therapy Oncology Group; GORTEC, Groupe d'Oncologie Radiothérapie Tête Et Cou; ICHNO, International Conference on Innovative Approaches in Head and Neck Oncology; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

* Corresponding author at: Department of Internal Medicine, Hematology, and Oncology, University Hospital Brno, Jihlavská 20, 625 00 Brno, Czech Republic.
E-mail address: szturz@gmail.com (P. Szturz).

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cancers, in whom the proportion of prognostically favourable human papillomavirus (HPV)-positive cases has been on the rise [1–3]. However, the majority of SCCHN patients still present with locoregionally advanced (LA) disease and require, irrespective of the HPV status, a multimodality approach, often integrating chemoradiotherapy either in the definitive or postoperative management. According to four large randomized trials, three cycles of high-dose cisplatin (100 mg/m^2) given once every three weeks concurrently with conventional external beam radiotherapy result in significantly better locoregional control and/or overall survival compared with radiotherapy alone and are at present considered the standard of care in this setting [4–7]. Notwithstanding such progress, the outcomes of nonsurgical treatment in LA-SCCHN have been rather disappointing both in terms of toxicity and efficacy. In this regard, our recent systematic review and meta-analysis provided a comprehensive evaluation of weekly low-dose versus three-weekly high-dose single-agent cisplatin given concurrently with conventionally fractionated radiotherapy. In the three-weekly arm, we included 31 prospective trials with accrual periods ranging from 1989 to 2013 and obtained the following results. Model-based estimates of 5-year overall survival, pooled rates of compliance defined as a proportion of those who received all three cycles, grade 3-4 mucositis (and/or stomatitis), and grade 3-4 dysphagia were 39% and 51%, 71% and 64%, 42% and 37%, and 26% and 20% in the definitive and adjuvant settings, respectively [8]. Therefore, research activities focusing on two important aspects, improving outcomes, most frequently by intensifying treatment, on the one hand and reducing adverse events on the other, have been warranted.

The conventional fractionation schedule consists of 2 gray (Gy) daily fractions delivered from Monday to Friday over 7–7.5 or 6–6.5 weeks to a total dose of about 70 or 60–66 Gy during definitive or adjuvant radiotherapy, respectively. Apart from adding concurrent chemotherapy, the treatment intensity can be increased by altering the dose intensity of radiotherapy. The latter is accomplished by a higher total dose given in the same time using two to three smaller fractions of 1.1–1.2 Gy per day (i.e. hyperfractionation). It is also possible to deliver the same (or slightly lower) dose in a shorter period of 5–6 weeks (or even faster) by extending the weekly treatment time usually to 6 days (i.e. acceleration). Both these approaches have been collectively referred to as altered fractionation radiotherapy. In addition, various combinations of hyperfractionation and acceleration exist. As an example, concomitant boost is characterised by a second daily fraction to a smaller, boost volume. A newer technique, simultaneous integrated boost, delivers different dose levels to different targets in a single fraction. Compared with conventional radiotherapy, altered fractionation confers a significant survival advantage of 3.4% at five years, favouring hyperfractionation (8% at five years) over acceleration (1.7–2% at five years) [9]. However, it seems that in the definitive setting, conventional radiation with concurrent chemotherapy yields better overall survival, disease-free survival, and locoregional control than altered fractionation radiotherapy alone, although at the cost of increased toxicity [10].

Consequently, a logical question arises as to whether combining altered fractionation radiotherapy with concurrent systemic treatment might further improve the outcome. In this respect, the Intergroup Radiation Therapy Oncology Group (RTOG) trial 0129 found no survival benefit from adding two cycles of three-weekly high-dose (100 mg/m^2) cisplatin to accelerated radiotherapy when compared with adding three cycles of the same high-dose cisplatin to conventionally fractionated radiotherapy [11]. Similar results came from the three-arm Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) trial 99-02, when the investigators evaluated accelerated chemoradiotherapy (70 Gy/6 weeks plus concurrent carboplatin/fluorouracil) versus conventional chemoradiotherapy (70 Gy/7 weeks plus concurrent carboplatin/fluorouracil) or even versus very accelerated radiotherapy alone (64.8 Gy/3.5 weeks) [12]. Of note, both trials employed acceleration, which most probably should not be the preferred form of radiotherapy intensification as alluded to above. From this perspective, intriguing data were presented from a network meta-analysis at the 2017 International Conference on Innovative Approaches in Head and Neck Oncology (ICHNO), suggesting that hyperfractionated radiotherapy with concurrent chemotherapy leads indeed to the longest overall survival among various other radiotherapy and chemoradiation regimens [13]. Nevertheless, not all patients may represent appropriate candidates for treatment intensification. Due to the markedly good prognosis of those with low-volume HPV-positive oropharyngeal cancer (e.g. T1-T3, N1-N2b) and at the same time low-intensity smoking history (< 10 pack-years), clinical trials investigating reduced-dose radiation and other de-intensification strategies are ongoing and need to be further explored [14].

In order to reduce treatment-related complications while maintaining high anticancer activity in the treatment of LA-SCCHN, weekly low-dose cisplatin regimens have often been combined with conventional radiation, replacing thus the standard, three-weekly high-dose cisplatin schedule. However, the adoption of the weekly low-dose approach in routine clinical practice has not been supported by evidence from adequately sized prospective randomized trials so far. In our previous work, we demonstrated that both approaches may differ to some extent in toxicity but probably not in efficacy. Hence, owing to the profound lack of hard clinical data on the side of the weekly regimen, the high-dose three-weekly regimen should remain the standard of care [8]. Herein, we focused on altered fractionation radiotherapy trying to resolve the same question: Is there any difference in efficacy, toxicity, and compliance between the two concurrent single-agent cisplatin regimens, a low-dose weekly or a high-dose given once every three to four weeks?

Methods

Search strategy

This systematic review and meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. A comprehensive search for full-text articles published in print or on-line up to December 1, 2015, was conducted from the National Library of Medicine (PubMed/MEDLINE), Web of Science, and Cochrane Central Register of Controlled Trials to identify prospective trials of patients with LA-SCCHN (stage III–IVB) who received altered fractionation radiotherapy concurrently with single-agent cisplatin. Restricting the language to English, the following keywords and their combinations were employed for the computer-aided literature search: “cisplatin”, “head and neck/oral cavity/pharynx/larynx”, “chemoradiotherapy/chemoradiation”, and “radiotherapy/radiation” (for detailed search strategy see Supplementary Methods). To retrieve studies of potential relevance for full-text assessment, the results were screened by title and abstract.

Selection criteria

Eligible trials investigated the altered fractionation chemoradiotherapy approach, i.e. hyperfractionation, acceleration, or a combination thereof, either (1) in the definitive setting as first-line treatment with curative intent or (2) post-operatively after curative resection of treatment-naive tumours. In the meta-analysis, we compared two concurrent single-agent cisplatin regimens. In the high-dose protocol, cisplatin at a dose of 100 mg/m^2 was administered every three (days 1 and 22) to four (days 1 and 28) weeks, whereas the weekly schedules were defined by a dose not exceeding 50 mg/m^2 and at least 4 treatment cycles. With the exception of radiotherapy fractionation, we applied the same exclusion criteria as used in our previous systematic review and meta-analysis [8]: retrospective studies; updates and additional investigations of previously reported patient populations, which did not add substantial new information on efficacy or