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Mini-review

Metronomic chemotherapy in head and neck cancer

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ABSTRACT

Head neck cancer (HNC) is generally treated with a multimodality approach. Loco-regional-distant control is often worst, due to the advantage stage disease at diagnosis and the optimal treatment option remains an unresolved issue. Metronomic chemotherapy (MCHT) is an emerging therapeutic option in clinical oncology and it may prove useful in HNC patients.

Introduction

Head and neck cancer (HNC) is a homogeneous group of rare malignancies, consisting of several primary anatomical subsites with an overall incidence of less than 450,000 new cases/year, worldwide [1]. Although HNC is rare, a detailed knowledge is important due to its high occurrence in select countries in which smoking and alcohol consumption represent the major risk factors [2]. However, over the last decades, it has been observed an increased risk associated with human papilloma virus (HPV) infections that identifies a distinct HNC subtype with significantly better prognosis compared to smoke and alcohol history HNC [3]. Overall, squamous cell carcinoma is the main histological type, accounting more than 90% of cases [4]. Patient's prognosis is highly variable and is determined by staging and baseline tumor characteristics. Despite significant progress in the conventional modalities of surgery (S), radiotherapy (RT) and chemotherapy (CHT), survival rates remain a significant problem, especially in locally advanced stage disease. In this setting of patients, 5-year overall survival is estimated to be worse (approximately 30%) and the prevalence of loco-regional recurrences (50%), as well as distant metastases (20%) stresses the importance of a more effective systemic treatment [5].

The addition of cetuximab to standard doses of platinum-fluorouracil chemotherapy for recurrent or metastatic HNC is associated with a significant increase in both overall survival ([OS] 10.1 months versus 7.4 months) and progression free survival ([PFS] 5.6 months versus 3.3 months) [6]. Although the response rate remains low (36%), this first-line treatment regimen is currently considered the standard of care in patients with recurrent or metastatic disease [4]. But cetuximab is an expensive drug and thus in resource-poor setting the use of this combination is limited [7]. Nowadays, there is considerable interest in innovative approaches, such as metronomic chemotherapy (MCHT) that could be essential in the near future in term of survival and cheapness. This review discusses current evidence and conceptual issues pertinent to MCHT in the management of HNC. There is hope that focus on MCHT may lead to development of new promising therapeutic strategies to ameliorate prognosis in HNC patients.

Search strategy

Data from all clinical trials, both published and ongoing, were included using literature electronic databases searching (Pubmed, Medline and clinical.gov) and hand searching (meeting proceedings of European SocieTy for Radiotherapy & Oncology,

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Table 1
Clinical trials on metronomic chemotherapy in head and neck cancer.

MCHT drug	Study	Year	Phase	Setting	Primary tumor	Patients (n)	Study design	Results
Celecoxib/methotrexate	Patil et al. [7]	2013	Prospective observational	Palliative	HNC	57	Celecoxib 200 mg twice daily/ methotrexate 15 mg/m^2	Median PFS 153 days; median OS 186 days
	Patil et al. [16]	2015	II	Palliative	HNC	57	Celecoxib 200 mg twice daily/ methotrexate 15 mg/m^2	Median PFS 101 days; median OS 249 days*
						53	Cisplatin 75 mg/m^2 every 3 weeks	Median PFS 66 days; median OS 152 days
	Patil et al. [18]	2016	Retrospective	Palliative	Maxillary sinus	5	Celecoxib 200 mg twice daily/ methotrexate 15 mg/m^2	Median OS 126 days
	Pandey et al. [21]	2016	Retrospective	Operable	Oral cavity	335	Celecoxib 200 mg twice daily/ methotrexate 15 mg/m^2	Median DFS 13 months; median OS 30 months
	Pai et al. [22]	2013	Retrospective matched-pair analysis	Operable	Oral cavity	32	Celecoxib 200 mg twice daily/ methotrexate 15 mg/m^2	2-year DFS 86.5% (94.6% in those who received ≥ 3 months MCHT)*
						32		2-year DFS 71.6%;
	Patil et al. [25]	2015	Retrospective	Palliative	Oral cavity	100	Celecoxib 200 mg twice daily/ methotrexate 15 mg/m^2	Median OS 110 days; 6-month OS 26.4%
Celecoxib/ methotrexate/ erlotinib	Patil et al. [19]	2016	Prospective observational	Palliative	HNC	15	Celecoxib 200 mg twice daily/ methotrexate 15 mg/m^2/ erlotinib 150 mg once daily	Median PFS 148 days
Methotrexate/ capecitabine	Mateen et al. [20]	2015	Prospective observational	Palliative	HNC	72	Methotrexate 2.5 mg twice in a week/capecitabine 500 mg twice a day	Median PFS 0.671 year; median OS 1.33 year
Tegafur/uracil	NCT00855881 [23]	Ongoing	II	Locally advanced	HNC	115	Tegafur-uracil 1 cap, bid for 1 year	N/A
Cetuximab/ cyclophosphamide	NCT01581970 [26]	Completed	II	Palliative	HNC	8	Weekly cetuximab/ cyclophosphamide 50 mg twice daily for 12 weeks.	N/A

MCHT: metronomic chemotherapy; n: number; HNC: head neck cancer; OS: overall survival; PFS: progression free survival; DFS: disease free survival; *: p-value <0.05; N/A: not available.

European Society of Medical Oncology and American Society of Clinical Oncology). A literature search was performed using the following combinations of terms: "metronomic chemotherapy", "continuous low dose", "head neck cancer", "advanced", "metastatic", "recurrent". The search was restricted to English-language manuscripts. Reference lists of previously published reviews were explored [8–10]. For clinical trials with more than one publication, only the latest version was included in the analysis. Search strategy was performed up to September 2016.

The concept of metronomic chemotherapy

The concept of MCHT is based on the hypothesis that the frequent administration of low doses (1/10th–1/3rd of the maximum tolerated dose [MTD]) of drugs, at shorter intervals without interruption, should be more effective in controlling tumor growth than dose escalation, especially in those patients that showed acquired drug resistance [11].

This concept has been implicated when MCHT was administered as successive lines of CHT in several advanced or metastatic diseases, including advanced breast cancer and recurrent ovarian cancer [12].

Briefly, there are three main mechanisms related to MCHT anticancer activity and efficacy. Firstly, continuous low doses administration of cytotoxic drugs may efficiently target tumor-associated neo-angiogenesis by affecting intratumoral vascular endothelial cells repair – anti-angiogenic mechanism – [13]. Secondly, MCHT can reduce the numbers of circulating regulatory T cells and therefore their inhibitory functions on antigen-specific immune response – immunomodulatory mechanism – [14]. Lastly, MCHT can promote tumor dormancy, secondary to tumor cells in G0-G1 arrest – cellular dormancy mechanism – [15].

Clinical studies

MCHT has been used in HNC mainly in two situations: in palliative setting and in radical multimodal approach. In this section, we will focus on the major studies in the use of MCHT. Table 1 reported a complete overview of MCHT clinical trials in HNC patients.

Palliative setting

Based on the promising results of the MCHT administration for palliative intent in rural centre near Mumbai, Patil et al. planned a prospective randomized phase II trial comparing MCHT to single agent cisplatin-based CHT, in patients with metastatic, relapsed or inoperable HNC [7,16]. In total 110 patients were enrolled. MCHT consisted of methotrexate 15 mg/m^2 weekly and celecoxib 200 mg twice daily; whereas cisplatin was given three weekly at 75 mg/m^2. Results showed a significant better PFS (249 days versus 152 days, $p = 0.02$) and OS (101 days versus 66 days, $p = 0.014$) in MCHT than cisplatin-based CHT. Quality of life (QoL) was not significantly different between the two treatment [17]. However, there was a statistically significant improvement in "pain" score from baseline to week 3 (OR = 3.14, $p = 0.036$) and week 6 (OR = 3.33, $p = 0.034$) in the MCHT schedule compared with the cisplatin regimen. Focusing on MCHT group, the vast majority of patients (n = 50; 87.7%) had tumor control, with complete response, partial response and stable disease in 2 (4%), 7 (14%) and 41 (82%) patients, respectively [7]. Globally, toxicity grade ≥3 was recorded in 5 patients, only. In a study published on maxillary sinus carcinoma, similar results have been noted [18]. After palliative MCHT, partial response was evident in 1 patient (25%), stable disease in 3 patients (60%), and progressive disease in 1 patient (25%). There were no grade ≥3 toxicities. To improve response rate, a new MCHT scheme