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The vicious circle of treatment-induced toxicities in locally advanced head and neck cancer and the impact on treatment intensity

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ABSTRACT

The intensity of the available treatment approaches for locally-advanced head and neck cancer (HNC) is at the upper limit of tolerance of acute toxicities. Several factors including breakthrough cancer pain, mucositis, dysphagia, local and systemic infections, and nutritional problems are related to treatment intensity. Particularly, pain, as symptom directly associated with the disease or combined with other treatment-related factors, has a major impact on quality of life of HNC patients and ultimately can influence the efficacy of treatments in HNC. Here, a Multidisciplinary Board of Italian Experts has addressed these issues, with the aim to identify the unmet need and appropriate strategies for the maintenance of optimal treatment intensity in HNC.

1. Introduction

Tumors arising from the head and neck are among the ten most common neoplasms worldwide (Siegel et al., 2017), and their incidence is increasing, with over 550,000 newly diagnosed cases each year (Ferlay et al., 2013). Nowadays the intensity of the current treatment approaches for locally advanced head and neck cancer (HNC) is at the upper limit of tolerance of acute toxicities. Conventional management strategies including definitive radiation with concurrent chemotherapy (CCRT) or biological therapy (cetuximab), surgery and adjuvant (chemo)radiation, or radiation given with altered fractionation schemes, are indeed associated with

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acute and long-term morbidity and impairment of patients' quality of life (QoL) (Kelly et al., 2016). Considering the raising intensity of therapy, the costs of treatments for localized HNC far exceed those for other aspects of care (Wissinger et al., 2014). Moreover, these highly toxic contemporary treatments have significantly improved the locoregional control in advanced head and neck cancer, but the effects on patients mortality have been modest, without a substantial extension of the overall survival (Corry et al., 2010). Evidence from recent trials have suggested that de-escalation of treatment regimens as well as tailored treatment strategies for selected, specific subgroup of HNC patients may achieve similar or even superior efficacy with less toxicity (Kelly et al., 2016; Corry et al., 2010).

However, the importance of maintaining treatment intensity remains a key factor for the success of the therapies in most combined approaches. Numerous negative factors contribute to the reduction of treatment intensity in HNC patients, including background and breakthrough cancer pain (BTcP), mucositis, dysphagia, local and systemic infections, and nutritional problems. All these factors, either alone or in different combination patterns, have also a major impact on QoL of HNC patients. At present, only modest attention has been paid, in clinical practice, to the correlation between those events and treatment intensity. To address this unmet need, a Multidisciplinary Board of Italian Experts (medical oncologists, surgeons, pain therapists, radiotherapy specialists) in the management of HNC has assembled with the aim to review relevant literature and identify strategies for the maintenance of optimal treatment intensity in HNC patients. Here we present the outcome of this Expert discussion.

2. Methods

The Expert Panel discussed the topics during two meetings, during which clinical experiences and literature were shared and reviewed. No formal techniques for the achievement of consensus were applied, but the discussion among Participants was handled by a professional facilitator.

During the first meeting, a series of keywords was identified: HNC; treatment intensity; treatment dose; pain; mucositis; infection; dysphagia; nutrition; education. Using these keywords, a systematic query-based MEDLINE search was carried out by a professional methodologist and editor in order to provide solid evidence on the topics of the review. No research limits were applied, but a focus was given on reviews and well-conducted studies published in the last 5 years. This search resulted in 126 papers; the Participants were offered the opportunity to revise the entire lists of papers and add others from their personal collection of literature. Papers were then selected for inclusion according to their relevance for the topic, on the base of Participants' and editor's judgment. A first draft of the paper was then prepared by the Participants, according to their clinical and research interests, and the editor; all Participants critically revised the manuscript over consecutive turnaround of revisions until a consensus on the final version was reached.

3. Treatment intensity: basic concepts

Treatment intensity in oncology field is considered as a defined dose of radiation and/or systemic therapy over a pre-specified time, aimed at controlling tumor growth with curative intent. This goal should be pursued by keeping in mind the QoL of patients, with a focus on pain, treatment-related toxicities, comorbidities, self-sufficiency, ability to complete daily activities and nutritional issues as well as patient's feeling and emotions concerning the disease and therapy. Importantly, most studies available to date do not distinguish between causes of dose reduction and those of treatment interruption and often specifications of adverse events leading to reduction in dose intensity are not fully reported; these issues largely limit available evidence on the topic. Moreover, in field-practice experience dose reduction is applied differently than in clinical trials, a setting in which defined rules for dose reductions are applied.

In patients with locally advanced HCN, the non-surgical standard of care is radiotherapy to a dose of 70 Gy with concurrent chemotherapy, as determined by a *meta*-analysis on 93 randomized trials over 17,000 patients (Pignon et al., 2009). Large portions of the pharynx and neck soft tissues receive high doses of radiation in patients undergoing standard management for HNC and the toxic effects are enhanced by radiosensitising chemotherapy. Therefore, numerous studies have explored the feasibility of reducing radiotherapy intensity or new technical delivery of radiotherapy; for instance, Chera et al. (Chera et al., 2015) investigated 60 Gy radiotherapy with concurrent low dose of chemotherapy in patients with human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma obtaining a high complete response and low toxicity. On the other hand, variations in radiotherapy protocols applied in several clinical trials suggest that total radiation dose and duration of treatment are both correlated with tumor control and survival. In particular, clinical evidence that interruptions adversely influence tumor control primarily comes from studies with planned treatment interruptions, also known as split-course therapy. Fesinmeyer and collegues (Fesinmeyer et al., 2010) described a statistically significant 68% increased risk of death associated with radiotherapy interruptions. This likely reflects a loss of tumor control caused by extended periods with no radiation delivered to the tumor. In addition, the tumor control rate has been estimated to decrease of at least 1% for each day of radiation treatment discontinuation (Russo et al., 2008).

Most of the randomized trials in HNC used cisplatin as chemotherapeutic agent at the dosage of 100 mg/m2, three times throughout the course of radiotherapy (cumulative dose of 300 mg/m2). Interestingly, lower doses of cisplatin (6 mg/m2 daily and 20 mg/m2 on day 1 and 5 of a 21-day cycle) administrated in combination with radiotherapy showed promising results in advanced HNC patients (Jeremic et al., 2000; Huguenin et al., 2004); similarly, some groups advocate the use weekly cisplatin as a strategy to increase dose intensity and/or reducing the frequency and severity of adverse events (Ho et al., 2008). However, so far no trial showed the superiority of one regimen over the other and accumulating evidence seem to point to the importance of reaching doses of concomitant cisplatin higher than 200 mg/sm, at least for HPV negative diseases (Spreafico et al., 2016).

One alternative strategy for reducing chemotherapy-related toxicity is the replacement of cisplatin with cetuximab, a monoclonal antibody targeting the EGFR extracellular ligand binding domain, which was shown to improve survival over radiotherapy alone (Bonner et al., 2006). Several trials comparing these 2 strategies are ongoing (NCT01302834–NCT 01874171–NCT 01855451 clinicaltrials.gov). Often, treatment-induced toxicities lead to interruptions and discontinuations of the therapies, which can have a negative impact on subsequent management of HNC patients.

Overall, whenever possible, strategies aimed at preventing, rather than managing, toxicities, should be instituted. On the other hand, a prompt management of all symptoms which may impair treatment intensity is paramount. The management of HNC patients should base on: i) identification of the patients at risk; ii) the prevention of symptoms, whenever possible; iii) individualized treatment; in addition, it requires expertise from different areas of competence that need to be integrated in the treatment process. In this light, an approach based on a multidisciplinary team (MDT) in a tertiary referral Center could add value in the management of HNC patients (Bergamini et al., 2016; Bossi and Alfieri,