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REVIEW ARTICLE

Induction chemotherapy in head and neck cancers - old actors, new horizons

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Summary

Head and neck squamous cell carcinoma (HNSCC) is the sixth worldwide cancer, with more than 650,000 new cases diagnosed each year. The current management of this pathology has evolved over time from surgery or radiotherapy as the only treatment method to a therapeutic association of methods with a modern management based on multidisciplinary loco-regional and systemic treatments. Cisplatin-based chemotherapy administered concurrently with radiotherapy is accepted as a therapeutic standard in locally advanced cases of HNSCC (T3, T4 or N +), these stages accounting for 60% of newly diagnosed patients. The use of induction chemotherapy (IC) has been used for over 30 years, the results being controversial. Currently, the association of taxanes with platinum-fluorouracil-based regimens has shown benefit in numerous studies. Gemcitabine also demonstrated radiosensitizing potential for administration as a single agent or associated with platinum salts. The introduction into the therapeutic arsenal of new molecular target agents or of immunotherapy as well as the development of irradiation techniques with toxicities reductions opens new horizons for the sequential administration of IC followed by radiotherapy as a single method or as a concurrent chemoradiation (CCRT).

Key words: *induction chemotherapy, head and neck cancers, radiotherapy, immunotherapy, surgery, toxicity, oncology*

Introduction

Head and neck squamous cell cancer (HNSCC) is the most common tobacco-related disease and accounts for more than 650,000 cases and 330,000 deaths annually, affecting almost 600,000 people worldwide each year. In Europe, 250,000 cases have been reported, which represent about 4% of the incidence of cancer, a value 1% higher than in the United States, the number of deaths being 63,500 in 2012. Historically, surgical treatment and later radiation therapy were the preferred methods of treatment. In the 80s of the last century the patients were treated with radiotherapy, especially in the case of relapse or tumors with advanced inoperable stages, but the results were disappointing. Radiation therapy obtained local control in 50% of the cases with 5-year survival less than 10%. If patients experienced relapse or persistent disease after treatment survival was less than 18 months in most cases. The main cause of therapeutic failure is the loco-regional recurrence that occurs in more than 60% of the cases and about 20% will develop distant metastases [1].

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Chemotherapy for HNSCC

Cipslatin is not a conventional alkylating agent, acting by introducing modifications of the DNA chains. The complex obtained by replacing chlorides with water reacts with the base N7 of guanine base. The entry into the cell is done with the help of a transporter and the exit of the agent from the cell is done with the help of another transporter. Discovered in 1965 by chemist Barnett Rosenberg cisplatin is active in cancers like head and neck, ovarian, cervix, breast but the maximal response rate is demonstrated in testicular cancer. The renal and cardiac toxicity of this agent is largely due to oxidative stress in the mitochondria. Toxic effects of cisplatin include ototoxicity, neurotoxicity, digestive toxicity, myelosuppression, nausea and emesis. However, the most important toxicity associated with organ dysfunction in over 30% of the cases receiving high doses is renal toxicity [2-3].

At that time, chemotherapy was used in palliative metastatic disease. With the advent of new chemotherapeutic agents, new concepts of chemotherapy use have been developed in the multimodal treatment associated with surgery or radiotherapy. Al Saraf mentions 5 concepts for the use of chemotherapy in head and neck cancers: induction chemotherapy, sandwich chemotherapy (interspersed between surgery and radiotherapy), adjuvant chemotherapy (defined as treatment following a definitive treatment regardless of whether it is surgical or radiotherapy). At that time, the researchers define "concurrent chemo-radiotherapy" not only a treatment administered simultaneously including chemotherapy and radiotherapy as a definitive treatment, but also the pre-operative and post-operative sequences. The 5th treatment class includes all of the above [1].

Generally, at an early stage, head and neck cancers are treated locally by surgery or radiotherapy, but most cases are locally advanced stages (III-IV). Even if at this stage of disease the prognosis is more unfavorable, the use of aggressive multimodal treatment offers a therapeutic potential. Chemotherapy has been introduced in the management of head and neck cancers to improve therapeutic rates and increase the rates of preservation of the tumor-affected organ. Cisplatin was the most commonly used therapeutic agent in concomitant administration due to its radio-sensitizing effect. The combination of cisplatin with radiotherapy has improved local-regional control and progression-free survival (PFS) in numerous studies. Regarding the administration of cisplatin in concomitant treatment with radiotherapy, the optimal treatment protocol is considered cisplatin 100 mg/m^2 on days 1, 22 and 43. Referring to the cumulative dose of cisplatin, there is already data in the literature demonstrating a cutoff of 200 mg/m^2 as the dose that is associated with a favorable response. It becomes feasible to hypothesize that 2 cycles of CRRT with 100 mg/m^2 cisplatin could be as effective as 3 cycles (300 mg/m^2 cumulative dose). Such a hypothesis would lead to reduced toxicity of chemotherapy especially of the kidney damage. Although there is evidence in this regard, there have been no randomized trials evaluating the efficacy of 2 cycles of 100 mg/m^2 of cisplatin as compared to 3 cycles. In 40% of the cases, the concomitant regimen with weekly administration of 30-40 mg/m^2 cisplatin the expected dose is 240-350 mg/m^2 [4-5].

In a study that included 314 patients, 127 patients (40.4%) were treated with cisplatin 100 mg/m^2 with a 3-week administration protocol and 187 patients (59.6%) received 40-50 mg/m^2 weekly. The authors concluded that several patients received a cumulative dose of cisplatin of at least 200 mg/m^2 in the group treated with the 100 mg/m^2 protocol at 3 weeks. The average cumulative dose was 200 mg/m^2 (between 150 mg/m^2 and 300 mg/m^2) in the case of the 3-week administration protocol and 160 mg/m^2 (between 120 mg and 240 mg/m^2) in the case of the weekly administration protocol. All patients received concomitant radiation therapy using the IMRT technique in total doses ranging between 66Gy-72Gy [4,6].

A trial that aimed to demonstrate the non-inferiority in which the locoregional control for weekly cisplatin (30 mg/m^2) did not reach its goal, since the final result was in favor of the 3-week regimen. The studies of Espeli et al and Rades et al demonstrated an overall survival (OS) improvement for the case when CCRT was administered with the protocol at 3 weeks, but the higher cumulative dose was associated with renal toxicity. Spearfico et al also considered HPV status, demonstrating that for patients with HPV negativity SCCHN, the cumulative dose of cisplatin of at least 200 mg/m^2 is a factor associated with a favorable outcome [7-9].

The most important toxicity of cisplatin is renal impairment but the adverse effects include also ototoxicity, neurotoxicity, digestive toxicity, bone marrow toxicity and nausea. Thirty percent of the patients receiving cisplatin in high doses will have renal toxicity. Platinum-based radiochemotherapy (CCRT) is currently the standard treatment in head and neck squamous cell carcinoma (SCCHN), in non-locally advanced or resectable cases, but considered with high risk of recurrence. CCRT is also used for resectable cases but inoperable due to comorbidities. The MACH-NC meta-analysis demonstrated the benefit of CRRT in these situations.

Analyzing 87 trials that included 16,485 patients Pignon et al have demonstrated the superiority of CRRT in relation to induction chemotherapy followed by radiotherapy. Currently, the results analyzing the benefit of induction chemotherapy followed by CCRT are controversial, except for the demonstrated benefit for some subtypes of oropharyngeal cancer and for bulky disease [10,11].

Recently, another chemotherapeutic agent has been used concomitantly with radiotherapy. Gemcitabine or 29, 29-difluorodeoxycytidine is a fluorinated pyrimidine nucleoside with antitumor activity and favorable toxicity profile, being used in the treatment of solid tumors including SCCHN.Gemcitabine has also demonstrated synergistic activity with radiosensitizing potential when it is associated with platinum salts. In order to become active, intracellular activation by phosphorylation of gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP) is required. Antitumor activity is based on blocking of an enzymatic chain that leads to polymerization of the DNA chain. dFdCTP can be maintained in plasma for up to 72 h and the main metabolite of gemcitabine, difluorodexiuridine (dFdU), may exist in the plasma within a few days after chemotherapy, even at low doses. This compound is thought to have a contribution in the radiosensitizing mechanism of gemcitabine [12-14].

Eisbruch et al were the first to report dose-limiting toxicities in the case of locally advanced SCCHN; 300 mg/m^2 administered weekly with radiotherapy led to high tumor control rates but high mucositis and severe dysphagia. In case of gemcitabine administration 50 mg/m^2 severe mucositis was developed after week 4 of treatment and persisted less after the end of treatment [15].

Analyzing in a systematic review 13 papers evaluating gemcitabine in the concomitant treatment of head and neck cancers Vanderveken et al concluded that a weekly administration to a dose below 50 mg/m^2 led to complete response in 86% with an acute mucositis rate of 38% and acceptable late toxicity. The authors highlighted the radiosensitizing potential of gemcitabine demonstrating that very low doses offer a good therapeutic ratio, without increasing the rate of toxicities (mucositis and severe dysphagia) [16].

In Pignon's meta-analysis, adjuvant and neoadjuvant chemotherapy did not show significant benefits; the systemic treatment added to the locoregional treatment showed a general benefit in OS of 4% at 5 years, proven only if the protocol was CCRT. One explanation could be that 16 out of 31 trials did not evaluate a standard treatment based on platinum doublets. For the 15 trials that were based on a platinum + fluorouracil (PF) induction protocol, the benefit was 5% at 5 years in favor of adding induction chemotherapy to the locoregional treatmentadministered as a single therapeutic method [11].

5-fluorouracil (5FU) is a nucleobase analog that is uracil in which the hydrogen at position 5 is replaced with fluorine. 5FU is part of the antimetabolite class and inhibits DNA synthesis by blocking the conversion of deoxyuridyl acid into thymidilic acid by the cellular enzyme thymidylated synthase. For 30 years the association of platinum salts with 5FU was the basis of induction chemotherapy in HNSCC.

Cisplatin 100 mg/m^2 (on the first day) and 5FU 1000 mg/m^2 daily, given as a continuous 24 h 5-day infusion every 3 weeks, is the most used PF induction chemotherapy protocol. With the introduction of taxanes in antineoplastic therapy, docetaxel and paclitaxel were included in the induction chemotherapy protocols. The benefit of a triplet combination of chemotherapy was a significant therapeutic benefit (11.0 months compared to 8.2 months for nonresectable tumors and 38 months vs. 13.2 for resectable tumors). The average OS was 18.8 months compared to 14.5 for non-resectable tumors and for resectable tumors the OS was doubled (71 months vs. 35) when the triplet protocol – fluorouracil, taxanes and platinum salts (TPF) was used. The most commonly used TPF chemotherapy regimen was docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 + 5FU 750 mg/m^2/day for 5 days [17,19].

Currently, the results show the ability of the TPF protocol followed by definitive radiotherapy to provide survival rates equal to radical surgery with an improvement in quality of life in the local cases of laryngeal and hypopharyngeal cancer. A laryngetomy-free survival rate of 28.9 versus 23.5% in the case of CCRT was achieved when using TPF induction. Up to 4.5 years after the treatment, OS was similar. At longer time intervals after treatment, OS results were in favor of induction, and an increased rate of deaths in the CCRT group could be explained either by the higher rate of distant failure, starting from the premise already demonstrated, that in advanced nodal disease TPF IC reduces the risk of distant metastases. Another hypothesis is that the deaths are related to an increased aspiration-related risk in the CRRT group [18,19].

Addition of cetuximab weekly to TPF (C-TPF) for four cycles resulted in response rates comparable to those obtained by the TPF protocol, with an average value of 86%. The rate of febrile neutropenia was about one in four patients, mucositis and diarrhea being other adverse effects. In order

to reduce the toxicities clinicians tried to substitute docetaxel with nab-paclitaxel (100 mg/m^2) and to reduce the continuous infusion with 5FU at 3 days. A better toxicity profile associated to immune checkpoint inhibitors anti-PD1/PDL1 makes it feasible to test immunotherapy in combination with induction chemotherapy [17,18,20].

Conclusions

IC based on the use of the TPF protocol tends to become an alternative to standard treatment (CCRT). In the absence of standardized and clinically validated biomarkers that predict sensitivity to platinum or other classes of systemic treatments, a regimen based on an association of 3 agents with different mechanisms of action appears to have a benefit in both tumor control and toxicity reduction associated with high dose of cisplatin. Recent evidence also claims that the cumulative dose of cisplatin > 200mg/m^2 is a predictor of favorable response to IC. The combination of target molecular agents with induction therapy has increased the rate of toxicities but an association with immunotherapy becomes a feasible option. Also, IC may be an early predictor of response to chemotherapy and can direct the treatment to intensify or de-escalation of radiation therapy in these cases. By reducing the size of bulky disease IC can convert the operability of some tumors or may lead to the de-escalation of radiation therapy in cases with complete clinical and imaging response. These strategies are currently being investigated in clinical trials that they aim to improve the quality of life of patients and at the same time increase the tumor control.

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Conflict of interests

The authors declare no conflict of interests.

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