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Review Article

Recent advances in chemotherapy for head and neck cancers

Uma C. Sambargi, Mahesh D. R., Anuradha Pai[1], Prathima Maligi[2], Ramanarayan B. K., Sanjay C. J.

Departments of Oral Medicine and Radiology, [2]Oral and Maxillofacial Pathology, Dayananda Sagar College of Dental Sciences, Bangalore, [1]The Oxford Dental College and Research Center, Bangalore, Karnataka, India

ABSTRACT

Systemic chemotherapy is increasingly being used with radiotherapy for the radical treatment of advanced head and neck cancers. Chemotherapy offers modest benefits in the metastatic setting. Platinum containing agents are the most active drugs and form the mainstay of most chemotherapy schedules. In recent years taxanes have shown activity in head and neck cancers and are being incorporated into neo-adjuvant and concomitant chemotherapy regimens. Targeted agents and epidermal growth factor receptor (EGFR) inhibitors, like cetuximab, in particular, have shown benefit in the metastatic and the concomitant setting. EGFR inhibitors and other targeted agents form the thrust of pre-clinical and clinical research into the systemic treatment of head and neck cancers.

Key words: Head and neck cancers, chemotherapy, concomitant and induction chemotherapy

INTRODUCTION

Surgery and radiotherapy are the mainstays of treatment for squamous cell carcinoma seen in the head and neck (SCCHN) of patients. In recent years, systemic chemotherapy has increasingly been incorporated into the treatment plan. As part of the primary treatment, systemic chemotherapy can be administered before (induction or neoadjuvant chemotherapy) or during (concomitant chemotherapy) radiotherapy (CRT). Adverse effects tend to be the limiting factors.[1] The mode of treatment for patients with squamous cell carcinoma of the head and neck depends on the site and stage of the disease, and on the overall health status of the patient. In most cases of stage I or II cancers, a single modality therapy of surgery or radiotherapy is considered.

Surgery is the initial treatment of choice. Before 1980, the initial treatment of patients with locally advanced stage III or IV (M0) would also have been surgery and / or radiation therapy, a choice that also depended on the site of the disease, the resectability of the cancers, and the performance status and comorbidities of the patient. However, because of the poor results obtained with 'traditional' therapy in this latter group, especially those with stage IV disease or unresectable cancers, systemic chemotherapy was introduced in the mid 1970s, as part of the combined modality treatment.[2,3]

Chemotherapy was used in patients with earlier disease stages and with resectable disease for organ preservation and better cure rates. Systemic chemotherapy was usually administered with palliative intent to patients with advanced stage IV disease, M1 cancers, or recurrent disease beyond salvage local treatment.[4]

EVOLUTION OF CHEMOTHERAPY

The treatment of patients with locally advanced head and neck cancers has evolved since the introduction of combined modality treatment for these patients. Initially, a single chemotherapeutic agent such as methotrexate or cisplatin was prescribed before local definitive treatment. After that, a combination of cisplatin and bleomycin was introduced, administered as a single course before local therapy. Later, two or three courses of cisplatin plus bleomycin were

Address for Correspondence:
Dr. Uma C. Sambargi,
Department of Oral Medicine and Radiology, Dayananda Sagar College of Dental Sciences, Shavige Malleswara Hills, Kumaraswamy-Layout, Bangalore – 560078, Karnataka, India.
E-mail: uma.sambargi@gmail.com

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given as part of the combined modality treatment. Methotrexate alone and / or vinca alkaloids (vincristine or vinblastine) were then added to the combination of cisplatin plus bleomycin[2,3]

In 1980, the combination of cisplatin and continuous infusion (96 – 120 hours) of 5-fluorouracil (5FU) was introduced, which has become a widely used combination chemotherapy in patients with squamous cell carcinoma of the head and neck. Also, at approximately the same time, the concept of concurrent chemotherapy with radiation therapy was revisited, with the introduction of cisplatin given concurrently with radiation therapy, as the primary treatment for patients with inoperable and / or unresectable head and neck cancers.[3]

During the last quarter of a century, clinical trials for patients with squamous cell carcinoma of the head and neck have demonstrated progress in treatment outcomes, including better local control, lower incidence of systemic recurrences, improved disease-free survival, and most importantly, improved overall survival. The quality of life has improved for many of these patients, especially when the larynx and voice function is preserved in cancers of the larynx or hypopharynx. Improvement in the overall survival was demonstrated by prospective randomized phase III studies and meta-analyses, and more significantly, by population-wide statistics. It is not generally recognized that the greatest decline in mortality rates, in the period 1990 to 1997, has occurred in patients with head and neck cancers. This decline was noted for patients both above and below 65 years of age, for both men and women, and for both blacks and whites.[5] With the introduction of new active chemotherapeutic agents and combinations, new agents given with radiation therapy, targeted treatments, and better sequencing of treatment options, it is expected that further improvements in treatment outcomes will follow.

METHODS OF TREATMENT

The two major indications for administering chemotherapy are as a single modality or as concurrent chemo-radiation therapy.

Induction chemotherapy

The rationale underlying the use of induction chemotherapy is that drug delivery is likely to be better in untreated, well-vascularized tumors; disease may be down-staged before definitive treatment and micrometastases may be targeted.[6]

Induction chemotherapy is used in clinical practice and is thought to be beneficial for reducing the rate of distant metastases,[7] increasing organ preservation.[8-10] Combination of cisplatin (75–100 mg/ m^2) and 5-flurouracil (5-FU, 750–1000 mg / m^2) every three weeks is the most commonly used regimen (PF) for induction treatment. The PF regimen yields a 5% improvement in a five-year survival. There have been three randomized trials adding taxanes to the standard sequential approach. In one randomized trial by Hitt *et al.*, paclitaxel was added to cisplatin and 5-FU in the experimental arm.[11] Although the response rates were better in the experimental arm there was no significant difference in the overall survival (51% versus 43%, $p = 0.063$). In the two recently published studies (EORTC24971 / TAX323 and TAX324 study), docetaxel was added to cisplatin and 5-FU (TPF) in the experimental arm, for induction treatment.[12,13]

The study by Vermorken *et al.* showed a survival benefit for the docetaxel arm, but the overall two-year survival (43%) was lower than the other reported studies using the sequential approach. However, this study exclusively included unresectable patients, and concomitant chemotherapy was not used. Therefore, it is difficult to draw any conclusions from this study as regards the benefit of taxanes in the patients treated using the sequential approach for loco regionally advanced SCCHN. Posner *et al.* has demonstrated a statistically significant two-year survival of 68% for the TPF arm versus 55% for the PF arm using the sequential approach, in advanced head and neck cancer. Taken together, these data suggest that induction treatment with two- and three-drug regimens will be increasingly used in the future. The use of induction chemotherapy has also been investigated in the postoperative setting. The Radiotherapy Oncology Group (RTOG) study 0024, a Phase II study of paclitaxel followed by paclitaxel and cisplatin for CRT, in resected SCCHN patients, showed comparable toxicity and improved outcomes, compared to the historical controls (RTOG study 9501) receiving postoperative CRT alone.[14] In spite of the published evidence, induction chemotherapy is not considered the standard of care in many institutions. There are several reasons for this. It is thought that induction chemotherapy delays CRT, which is thought to be the definite treatment in advanced SCCHN. Second, the toxicity resulting from induction chemotherapy may preclude the delivery of adequate doses of chemotherapy and radiation during CRT. Third, some of the clinical trials with induction chemotherapy did deliver concomitant chemotherapy[15] and if they did it was thought to be suboptimal.[16] Randomized studies of induction chemotherapy followed by CRT versus CRT alone are ongoing and this should help clarify the role of induction chemotherapy for head and neck cancer.[17]

Concomitant chemotherapy

Concomitant chemotherapy during radiotherapy improves the locoregional control rates and survival.[18]

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In addition, combining chemotherapy with radiation improves the rates of organ conservation.[19] The meta-analysis by Pignon *et al.* has shown that cisplatin-containing concomitant chemotherapy conferred maximum benefit in patients with SCCHN, when used as a first-line treatment in the radical setting. Single agent cisplatin is the cytotoxic agent of choice for CRT. Cisplatin acts by forming intra- and interstrand DNA adducts, resulting in the inhibition of DNA synthesis. Cisplatin potentiates the effect of radiation by inhibiting a repair of the sublethal damage, by homologous and non-homologous DNA repair mechanisms.[20] The fact that this effect is not tumor-specific is supported by the increased acute toxicity seen in the concomitant chemo-radiotherapy regimens. Two seminal studies that have demonstrated the benefit of CRT using cisplatin 100 mg / m^2 on days 1, 21, and 43 of CRT, showed significant increased toxicity for the CRT arm;[21,22] 70 – 80% of the patients tolerated the three cycles of chemotherapy. Therefore, most cancer centers use a less toxic schedule, with either two cycles of cisplatin[16] weekly, low dose cisplatin or single agent carboplatin,[23] in order to improve patient compliance. The combinations of paclitaxel and carboplatin delivered weekly, 5-flurouracil (5-FU) and carboplatin and 5-FU and mitomycin-C, are the other active combinations in this setting.[24-27] In a recently reported Phase II study, high-dose, intra-arterial (IA) cisplatin and concurrent radiation therapy (RADPLAT) has been used in the treatment of 67 patients with stage IV head and neck cancer. RADPLAT involves infusing cisplatin directly into the tumor bed IA, while minimizing the effects of the drug systemically by using simultaneous intravenous infusion of sodium thiosulfate, a neutralizing agent for cisplatin. The use of the neutralizing agent allows delivery of a dose of cisplatin, of a magnitude of up to five times the standard dose. The RADPLAT regimen was found to be tolerable, with a two-year overall survival of 63%.[28]

The uptake of this regimen has been limited due to technical issues with IA drug delivery. The EORTC and the RTO 95-01 studies have shown improved disease-free survival, locoregional control rates, and overall survival (EORTC), in high-risk patients receiving CRT following radical surgical resection.[29] Both trials have used cisplatin as the chemotherapeutic agent. Patients with extra-capsular spread in the involved cervical lymph nodes and positive surgical margins have obtained the maximum benefit from postoperative CRT. Postoperative CRT is now the standard of care for high-risk patients, as defined by these studies.

Newer targeted agents

Epidermal growth factor (EGFR) overexpression has been shown to result in adverse outcome in head and neck cancer.[30] Bonner *et al.* has reported on a randomized trial of cetuximab, a monoclonal antibody against EGFR, combined with radiotherapy versus radiotherapy alone.[31,32] The study showed significantly improved disease-free survival locoregional control rates and overall survival in the experimental arm. Toxicity in the two arms was comparable in the two arms except for a higher incidence of acneiform rash and infusion reactions in the cetuximab arm. However, the use of concomitant cetuximab has, in practice, shown higher mucosal and skin toxicity compared to the Bonner study results.[33-35] Lapatinib, a small molecule inhibitor of tyrosine kinases associated with EGFR and human EGFR type 2 (HER2) has shown activity in SCCHN and is undergoing Phase III trials, in combination with CRT.[36] The anti-tumor effect of the EGFR inhibitors is due to the effect on the signal transduction pathways, which leads to inhibition of cell proliferation. It has been postulated that these agents also have an indirect effect on the inhibition of DNA repair, which might explain their efficacy in combination with radiation. However, the EGFR inhibitors can also inhibit the radiation-induced DNA repair in normal tissue, causing increased acute toxicity and radiation-induced carcinogenesis. Combining chemotherapy with tyrosine kinase inhibitors makes scientific sense as both agents are active in head and cancer and have different mechanisms of action. The proof of principle was obtained in a Phase III study of first-line cisplatin plus cetuximab, which showed improved overall survival in metastatic head and neck cancer patients.[37] Wirth *et al.* investigated the feasibility of combining panitumumab, carboplatin, and two dose levels of paclitaxel, with radiation, delivered using intensity modulated radiotherapy, as a primary treatment for patients with advanced SCCHN.[38] The incidence of grade 3 mucositis and dysphagia was greater than 94%. In addition 34% of the patients had a treatment break due to toxicity. Kies *et al.* combined cetuximab with paclitaxel and carboplatin for induction treatment followed by cisplatin-based CRT in a Phase II trial. The regimen was found to be tolerable with response rates that were comparable to the historical controls.[39] In a similar Phase I study, Haddad *et al.* found cetuximab plus TPF to be safe and tolerable for induction treatment, with 100% response rates in 28 patients.[40]

CONCLUSION

There is increasing clinical evidence proving the benefits of chemotherapy in the neo-adjuvant, concomitant, and the adjuvant (postoperative) setting, albeit at the cost of higher treatment-related toxicity. Newer radiation techniques, like intensity modulated radiotherapy, have the potential to reduce the toxicity, by reducing the radiation dose to the normal tissues. Novel targeted

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agents have the potential to enhance the therapeutic index by improving the outcomes and reducing toxicity.

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