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Neoadjuvant Chemotherapy in Squamous Cell Carcinomas: A Systematic Review

Priya Manimala

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ABSTRACT: Locally advanced SCCHN (LA-SCCHN) is generally treated by a combination of chemotherapy, irradiation and/or surgery. Timing of the chemotherapy has for long been a matter of debate but concurrent chemoradiation was widely adopted as standard of care for locally advanced squamous cell carcinoma of the head and neck after the publication of a large meta-analysis which demonstrated that concurrent chemoradiation confers an absolute survival benefit of 8%at 2 and 5 years. Induction chemotherapy has some appealing advantages including the opportunity of assessing tumor response and selecting the patients who are candidates for organ preservation. The cisplatin–fluorouracil combination has been the induction regimen of choice for two decades but has recently been superseded by a combination of cisplatin, fluorouracil and a taxane which can be considered the standard regimen when induction chemotherapy is appropriate. Multiple large randomized trials designed to compare sequential induction, i.e., chemotherapy followed by CRT to CRT alone are currently underway. New challenges are the integration of targeted therapies into the current treatment strategies and the identification of prognostic biomarkers and of factors predicting the response to treatment which would help to select patients who are likely to benefit most from induction chemotherapy.

I. INTRODUCTION

Oral cancer is the major public health issue which is responsible for 3-10% of the cancer mortality worldwide. The Indian subcontinent accounts for one third of the world oral cancer burden and the oral cancer ranks among the top three types of cancer in India[1,2] Oral squamous cell carcinoma (OSCC) is the most common malignant tumor, which is treated with surgery in the early stage and with comprehensive treatment including surgery, radiotherapy and chemotherapy in the late stage. Currently, surgical procedures include extensive resection of the primary lesion and appropriate neck dissection. Due to the high frequencies of lymph node metastasis (LNM) and distant metastasis (DM), which are the common consequences of tumors[3],the prognosis of OSCC patientsremains poor, with a high local recurrence rate and a 5-year survival rate of 50%.[4]Neoadjuvant Chemotherapy is mainly used for the treatment of advanced oral cavity cancer. Induction chemotherapy decreases the distant recurrence rate from 38–14% in advanced OSCC [5], while chemoradiotherapy only decreases the local recurrence rate and seems not to have any impact on distant metastasis [6]The term "neoadjuvant therapy" (NAT) is usually applied to a number of therapeutic modalities, which are administered before the surgical intervention in order to reduce tumor volume. Historically, preoperative therapy was used to convert inoperable tumor into surgically curable condition [7]

HISTORY OF NEOADJUVANT DRUGS: LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA HEAD & NECK

Two-thirds of the SCCHN are in a locoregionally advanced stage at diagnosis. Locally advanced SCCHN (LA-SCCHN) is generally treated by a combination of chemotherapy, irradiation and/or surgery [8]. One of the most surprising aspects of chemotherapy in advanced head and neck cancer is the sensitivity of squamous cell carcinoma to such therapy, in particular when administered in previously untreated patients, as in the case of the neoadjuvant setting. In the 1990s, many clinicians used neoadjuvant chemotherapy with the hope of reaching a better local control, or to improve survival, even though this was not evident from randomized studies [9]. It was only after the publications of promising data on chemoradiation and the individual patient-based meta analysis that the general attitude towards neoadjuvant chemotherapy has changed[10]. After ~20 years of conflicting results from chemotherapy in randomized trials in advanced head and neck cancer, three meta analyses reviewed its use. All three concluded that chemotherapy was associated with a statistically significant advantage in survival, but that this was low (4% absolute benefit at 2 and 5 years. In addition, during the years of clinical research, more and more sophisticated imaging tools have been introduced with major improvements in correctly staging tumors

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according to the TNM (tumor–node–metastasis) classification. This has been particularly the case as far as nodal extension is concerned. Moreover, although specific computed tomographic radiographical characteristics of metastatic nodes were reported to be clearly associated with different chemosensitivity and prognosis of patients treated with neoadjuvant chemotherapy, this adjunctive information was never utilized for optimizing patients selection criteria[11]Timing of the chemotherapy has for long been a matter of debate[12]Concurrent chemoradiation conferred an absolute survival benefit of 8% at 2 and 5 years although the benefit might be age dependent[13]

Table 1 Pros and cons for neoadjuvant therapy and primary surgery

Pros and Cons	**Neoadjuvant therapy**	**Primary surgery followed by adjuvant therapy**
Advantages	▪ May convert inoperable tumor to surgically curable condition ▪ May reduce the extent of surgery (preservation of the affected organ; lowering the risk of perioperative morbidity ▪ NAT allows to evaluate short-term response to a given therapy and change the treatment scheme if alternative options are available ▪ Early control of systemic cancer disease ▪ Excellent tool for translational research and accelerated approval of novel therapies	▪ Immediately removes the gross tumor bulk, thus significantly diminishing the population of potentially metastatic cancer cells and the probability of evolving drug-resistant clones ▪ Reliable visual inspection of the tumor spread during surgery ▪ Strong experimental evidences for potential efficacy of adjuvant therapy
Disadvantages	▪ Persistence of gross tumor bulk during a few months of therapy may increase the probability of forming metastatic clones even in case of gradual tumor shrinkage ▪ NAT is usually mutagenic, therefore it may facilitate tumor evolution ▪ May result in selection and expansion of resistant tumor clones ▪ Small tumor foci may be missed during the surgery and therefore remain in the body	▪ Extensive interventions are associated with increased rate of surgical morbidity and mortality ▪ Adjuvant therapy is often delayed due to perioperative complications ▪ Adjuvant therapy is given without prior in vivo test

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Beyond cisplatin–fluorouracil

Multiple researchers attempted to improve on the PF regimen since its introduction in the early eighties by the investigators at Wayne State University, who originally administered two cycles and observed an overall and complete response rate of 88% and 19%, respectively. By adding a third cycle and prolonging the 5-fluorouracil infusion to five instead of 4 days, overall and complete response rates went up to 93% and 54%, respectively [14]PF can be intensified by increasing the cisplatin dose and by modulating 5 fluorouracil with leucovorin.The PFL regimen consists of cisplatin 25 mg/m2/day on day 1–5, 5-fluorouracil 800 mg/m2/day on day 2–6 and leucovorin 500 mg/m2/day on day 1–6 [15]Vokes et al. [16,17]added interferon alfa-2b to aslightly different PFL regimen consisting of cisplatin100 mg/m2 on day 1, 5 fluorouracil 640–800 mg/m2/day on day 1–5 and oral leucovorin 100 mg every4 h on day 1–6 (PFL-If). The complete clinicalresponse rate after 3 cycles PFL-If was 51%. Othershave intensified the PF regimen by shortening thetreatment interval to 14 days. Franchin et al. [18]using that strategy observed an overallresponse rateof 88% with 16% completes responses.Shin et al. [19]combined ifosfamide, paclitaxeland carboplatin as induction regimen and reported an overall response rate of 81% and a complete response rate of 31% after 4 cycles. Definitive local treatment in that study was given based on the investigators preference. Disease-free 1- and 2-year survival rates were 88% and 77%, respectively, which was beyond expectation.Faivre et al. [20] administered PF biweekly for 3 cycles followed by two cycles of bleomycin, methotrexate and hydroxyurea and obtained an overall response rate of 71.4% after PF and 88.8% after the entire induction chemotherapy. Complete response rates were 17.1% and 33.3%, respectively.

Therapeutic study

The potential therapeutic benefits of neoadjuvant treatment incorporating immunotherapy primarily include early selection of treatmentresponders and cytoreduction to minimize the degree of oncologic resection in patients requiring definitive surgery – which may have important functional and cosmetic implications. Similarly, pre-operative cytoreduction may reduce the likelihood of a positive resection margin and could facilitate de-escalation of adjuvant post-operative radiation and/or chemotherapyin surgical patients. Data from pre-clinical models suggests that priming an immune response may also be superior in the neoadjuvant setting[21], which leads to speculation about early targeting of immune mechanisms in treatment naïve patients. Additionally, neoadjuvantimmunotherapy may downstage previously unresectable disease to becomeresectable disease and hasthe potential to provide early systemic therapy to address the risk of distant metastatic spread – a notion of particular concern in HPV-associated disease where distant relapse is the most common type of disease recurrence, and can occur late [22]

Discoveries

Aside from therapeutic benefits, neoadjuvant trials offer the opportunity for research and biomarker discovery. Using immune therapyafter biopsy confirmation of disease, but prior to definitive surgery, offers a window phase of treatment in which to deliver therapy and assess clinic radiologic and biologic response. Sequential biopsies allow for correlative studies aimed at understanding changes in tumor-immune metrics and permits correlation with response. Multiparametricflow cytometry, immunohistochemistry, and multiplexed immunofluorescence can be performed to quantify immune cells and immune checkpoint receptor expression patterns while the latter canprovide insight about spatial tumor-immune cell interactions. Wholeexome and RNA sequencing platforms can be applied to understand genomic determinants of immune cell function, facilitating neoantigen prediction modeling and protein expression analysis. Additionally, T cell receptor (TCR) clonotyping can determine unique gene rearrangement sequences that arise in response to antigen presentation in the lymphocytes infiltrating an individual tumor, and extra- or intracellular cytokine levels can be quantified to understand immune cell signaling. These methods can be interpreted together to understand the dynamic and complex tumor immune network and how it changes in response to administration of immunotherapy[23]

II. CONCLUSION

Thusneoadjuvant chemotherapy in technically unresectable HNC patients can make the disease resectable in around onethirdof the patients. The patients who could undergo surgery after neoadjuvant chemotherapy had significantly

improved survival as comparedto those who could not. The selection of these patients should be done by a multi-disciplinary team and all efforts should be done tomake disease resectable to achieve optimal outcomes.

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