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Controversy

The current role of systemic chemotherapy in the primary treatment of head and neck cancer

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ABSTRACT

The treatment of patients with locoregionally advanced squamous cell carcinoma of the head and neck (HNSCC) is still evolving into the perfect combination of the different multidisciplinary approaches. Induction chemotherapy (ICT) prior to planned definitive local therapy is widely used in this patient population for over 30 years but it is still unclear how to incorporate ICT into multimodality treatment the best. It appears to have a role in selected clinical situations especially for those patients with high risk for distant metastasis. However, since ICT protocols in different studies varies a lot, a comparative and consistent statement of benefits is difficult.

We show the recent developments including randomized trials comparing radiochemotherapy (RCT) and ICT followed by definitive RCT here. This review summarizes how ICT has developed over the years, provides critical remarks of recent developments, and discusses how clinical trials including ICT should be conducted in the future.

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) accounts for approximately nine percent of all cancer types in the world and has estimated 400,000 incident cases and 223,000 deaths during 2008 [1]. Treatment strategies for HNSCC have changed a lot in the last 30 years. Most of the patients present with locoregionally advanced diseases at diagnosis (LA-HNSCC). In contrast to early stage disease, these patients require comprehensive, sequential, multi-modality treatment regimens including surgical resection, chemotherapy, and radiotherapy. Non-surgical procedures are usually performed in unresectable tumors or in order to preserve organ and function. The gold-standard here is still the cisplatin-based concurrent radiochemotherapy (RCT) [2]. In 2009, a large meta-analysis of the use of chemotherapy in head and neck cancer was updated confirming the benefit of chemotherapy given as concurrent RCT, induction chemotherapy (ICT), or adjuvant treatment in patients with locoregionally advanced tumor. The results showed a modest survival benefit for ICT compared to RCT alone, which was not statistically significant [3]. The role of induction chemotherapy prior to definitive locoregional therapy for locally advanced HNSCC remains controversial since no consensus guidelines are available for its use. With the introduction of taxanes the historically tested cisplatin and 5-fluorouracil (PF) as induction agents were complemented. Two major randomised trials have suggested a higher response rate with the addition of docetaxel (T) to PF chemotherapy (TPF) [4,5]. In general, ICT is regarded as an effective way to not only shrink locally advanced malignancies and therefore to allow more effective and less toxic local therapy, but also potentially reduces distant metastatic disease because of systemic exposure. Definitive data in the literature from direct comparisons of ICT versus platinum-based RCT, which mostly showed no demonstrable benefit of ICT followed by concurrent RCT over concurrent RCT alone are controversial due to the lack of power in the statistical design or due to heterogeneity in the chemotherapy protocols used for induction and/or radiation therapy. As long as there will be no clear randomized studies with statistical power, the beneficial effect of ICT is still under discussion. This review summarizes how ICT has evolved over the last years including the recent results of direct comparing studies comparing to RCT, and discusses how the role of ICT in head and neck cancer may develop in the future.

Historical development of induction chemotherapy protocols in head and neck cancer

The rationale behind the induction chemotherapy concept originally included several considerations:

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- Yielding higher concentrations of chemotherapeutic drugs in tissue by optimized delivery through a vasculature that has not been disrupted by prior surgery or radiation.
- Reducing distant metastasis by high effective polychemotherapy.
- Assessment of tumor responsiveness and altering subsequent therapy according to response: organ preservation in good-responding disease. In case of no response: using salvage surgery in a non-irradiated tissue environment avoiding high risk of fistula or wound healing complications.
- Improved function pre radiation through tumor shrinkage and mucosal healing prior to radiotherapy; reducing tumor volume for subsequent radiotherapy.
- Potential predictor for radiosensitivity.
- Reduction of enhanced radiotoxicity observed in concomitant radiochemotherapy.
- Exploiting different tumorbiological point of attack than radiotherapy.

Various models of induction chemotherapy have been used over the years with different approaches and agents. One of the goals has been to improve the remission rates yielded with concurrent RCT and thereby improving disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS). Since at 2 years after treatment with concurrent RCT approximately 20% of the patients with locally advanced disease have distant metastasis, to improve the distant control was one of the important purposes of induction chemotherapy trials [6]. Beside this, the concept of organ preservation was also a reason to perform ICT. The Veterans Administration Laryngeal Study Group trial compared ICT followed by definitive radiotherapy (RT) to conventional laryngectomy and postoperative radiation in 332 patients with stage III or IV laryngeal cancer and demonstrated larynx preservation in two-thirds of patients who survived in the ICT arm [7].

However, until now the interpretation of crucial trials has been difficult because of their heterogeneity. Before implementation of docetaxel, an anti-neoplastic agent that disrupts the cell microtubular network which is essential for mitotic and interphase cellular functions, the most common ICT protocol was PF. Besides this combination diverse protocols which included other platin-containing combinations, multiagent chemotherapies without platin or single-agent chemotherapies (e.g. methotrexate) were described [6]. A large meta-analysis showed that ICT in this era was associated with a reduced risk of distant metastasis (HR 0.73; 95% CI, 0.61–0.88) although there was only a trend to survival benefit with ICT (2.4% at 5 years, HR 0.96; 95% CI, 0.90–1.02; $p = 0.18$). The survival benefit of RCT is mainly attributed to improved locoregional control, whereas ICT has more impact on distant metastasis (hazard ratio, 0.88; 95% CI, 0.77–1). However, there was a significant benefit for survival ($p = 0.01$; HR 0.88, 95% confidence interval 0.79–0.97) when the analysis was limited to only PF induction regimens [3].

The benefit of adding taxane to PF protocols was confirmed by three randomized phase III trials [4,5,8]. In the TAX323 study, 358 patients with unresectable, locally advanced stage III and IV tumors and a good performance status received either docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and 5-fluorouracil 750 mg/m^2/day continuous infusion day 1–5 (TPF) or cisplatin 100 mg/m^2 on day 1 and fluorouracil 1000 mg/m^2/day on day 1–5 (PF). These regimens were administered every 3 weeks for four cycles. Within seven weeks after ICT, patients who did not have progressive disease received radiotherapy alone. The median PFS and OS was significantly longer in the experimental group (11.4 and 18.6 months) than in the control group (8.3 and 14.2 months), respectively [5].

In the American trial (TAX324) 501 patients with stage III or IV disease, which was considered to be unresectable or were candidates for organ preservation, were randomly assigned to TPF (docetaxel 75 mg/m^2 on day 1, cisplatin 100 mg/m^2 on day 1, and 5-fluorouracil 1000 mg/m^2/day on days 1–4) or PF protocol (cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil 1000 mg/m^2/day on days 1–5). Three cycles were planned every 3 weeks.

Instead of undergoing radiotherapy only after induction chemotherapy, all patients received concurrent chemoradiotherapy with weekly carboplatin at an area under the curve (AUC) of 1.5 [4]. The median OS was 71.6 months in the TPF group and 34.8 months in the PF group ($p = 0.006$). Progression-free survival was also significantly better in patients treated with TPF (median 38.1 months vs 13.2 months). The local, locoregional, and distant failure did not differ significantly [9]. However, in a subgroup analysis of laryngeal and hypopharyngeal cancer the laryngectomy-free survival was significantly greater with TPF than with PF [10].

In the setting of organ preservation the GORTEC group also showed an improved larynx preservation in patients treated with TPF instead of PF but without gain in survival [8]. It is important to mention that salvage surgery, especially in the larynx, maintains overall survival. The more important endpoint in these studies should include laryngectomy-free survival or progression-free survival. The GORTEC protocol was similar to the TAX 323 but with only three instead of four cycles. This means a dose reduction during ICT, which might also explain the missing improvement of survival in this study. Responders to ICT received either RT alone or RCT.

All studies reported better compliance and quality of life with the TPF regimen compared to the PF regime. Although there are discrepancies concerning treatment protocol and dose in these studies, TPF became a standard of induction chemotherapy since the response and survival rate was superior to PF alone.

To evaluate the recent standard with TPF ICT a meta-analysis was published by the MACH-NC group (meta-analysis of chemotherapy in head and neck cancer group) [11]. Five randomized trials representing 1772 patients were included. In addition to the 3 already mentioned studies they included two other trials from Spain [12,13]. All trials compared PF versus PF plus taxane in stage III-IV HNSCC, except for TTCC 2002 [13], which was a three arm trial (PF vs TPF vs RCT). TPF induction chemotherapy improved OS and PFS in comparison to PF induction chemotherapy, with an absolute benefit at 5 years of 7.4%, from 35.0% to 42.4%, and of 7.1%, from 28.4% to 35.5%, respectively. Data for locoregional and distant failure from all patients were missing for one trial [12] and 25–30% of the patients in two other trials [5,13]. The analyses were conducted without these patients and showed an absolute decrease of locoregional failures of 7.4% at 5 years, from 51.6% to 44.2%, and an absolute decrease of distant failures of 6.4% at 5 years, from 20.1% to 13.7% in favor of the TPF protocol. The included trial were heterogeneous in terms of induction chemotherapy regimens (TPF using docetaxel or paclitaxel), concomitant therapy regimes (cisplatin versus carboplatin versus none), local extensions (resectable versus unresectable), or treatment settings (organ preservation versus definitive treatment). However, the benefit of TPF over PF does not seem to vary with the taxane used the trials. In summary, this meta-analysis showed that TPF significantly improves OS, PFS, and locoregional and distant failure compared with PF for locally advanced HNSCC, with the limitations given by the heterogeneity and some missing data. However, the direct comparison to RCT was still missing.

Studies comparing ICT to RCT

Focusing on this crucial question, several groups conducted trials to investigate these two different approaches. The prementioned Spanish group around Hitt compared TPF vs. PF vs. RCT in an open label three arm study [14]. 439 patients with stage IV HNSCC were randomly assigned to ICT with TPF (155 patients), ICT with PF (156 patients), and RCT alone (128 patients). TPF ICT