Integrating systemic agents into multimodality treatment of locally advanced head and neck cancer

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Although highly debated in the 1980s, randomized clinical trials have provided undeniable evidence that systemic chemotherapy, as part of a multimodality treatment collaboration, is effective in improving survival, organ preservation and local–regional control in locally advanced head and neck cancer (HNC). We are entering an exciting period in which new chemotherapy agents, new paradigms of treatment, new surgical and radiation technology, and new prognostic factors are rapidly becoming available. Information on how to integrate these new tools and on how they affect long-term outcomes are lacking, making decision making and treatment planning more difficult. With unprecedented survival and the changing demographics of HNC we must now consider long-term consequences in addition to survival and local and regional control as important factors in therapeutic decision making. The availability of different treatment plans that incorporate systemic chemotherapy, radiotherapy and surgery give us many tools with which to craft a treatment for each individual patient. Today, in this exciting and chaotic period, a multidisciplinary and collaborative approach for each HNC patient at the start of decision making and planning is a necessity and the absolute standard of medical treatment for excellent patient care.

Key words: chemoradiotherapy, chemotherapy, head and neck cancer, radiotherapy

The general principles of systemic chemotherapy in head and neck cancer

A decision on when and how to integrate systemic chemotherapy into the treatment of any individual patient is a critical part of planning for almost all patients with head and neck cancer (HNC) today. The multidisciplinary team must evaluate the patient, the tumor and the goals as part of that process. Even the experienced clinician is faced with significant clinical challenges in making decisions regarding therapy hence collaboration and experience are important to the process. Even with solid data from clinical trials, the available treatment options are subject to considerable differences of opinion; there is site-specific heterogeneity in biology, prognosis and therapy; functional deficits from therapeutic choices can be considerable and are part of the therapeutic and individual assessment; and selection of an appropriate treatment plan that suits the needs and condition of an individual patient can be difficult. Finally, increasingly aggressive non-surgical therapy results in substantial acute and long-term toxicity that requires considerable physician management and experience [1–2]. Nonetheless, treatment of HNC is associated with increasing rates of cure, functional organ preservation and a changing demographic of younger healthier patients, all of which have resulted in substantial improvements in survival outcome and clinical benefit [3].

Patient factors such as age, performance status, behavior and co-morbidities have to be taken into consideration in the planning process. Clearly the choice of agents and the intensity of treatment have to be aligned with the patient’s condition. Patients must be able to tolerate therapy physically and psychologically; intensity must be adjusted based on these factors. Tumor factors include site, stage, operability and molecular prognostic factors. Careful staging with a careful assessment of operability and consequences of surgery are absolute requirements for good decision making. Tumors of the oral cavity and sinuses are generally less responsive to chemotherapy and more amenable to a surgical approach with functional preservation [4–5]. Oropharynx, larynx and hypopharynx are sites more appropriately treated with an organ preservation approach that includes systemic chemotherapy at the outset and reserves surgery for salvage or complementation, e.g. for persistent nodal disease [6–11]. Oropharyngeal cancers can be divided into two diseases based on the molecular markers human papilloma virus (HPV) and p16 [12–13]. Tumor HPV and p16 expression are major prognostic indicators for oropharyngeal cancer and will become a standard test for prognostic and treatment decisions for this tumor. Unprecedented survival is being reported in patients with HPV-positive oropharyngeal cancer (HPVOPC), as opposed to environmentally related oropharyngeal cancer (EROPC), raising important and difficult questions about the long-term consequences of therapy. Finally, the goals of therapy are...
important. Functional organ preservation (FOP), local–regional control (LRC), prevention of distant metastases (DM) and overall survival (OS) are complex goals with important subtleties. LRC is not synonymous with FOP or OS. Treatment decisions for local–regional disease, which are the immediate focus of surgical and radiation oncologists, should include careful attention and knowledge of the risks for systemic failure and late morbidity based on stage, site and treatment planning, and consider the potential to benefit from systemic chemotherapy on all three outcomes.

Systemic chemotherapy can be delivered in different settings as part of a multimodality plan and with different intent. For example, postoperative chemoradiotherapy (PO-CRT) is indicated for patients with poor prognostic features in the pathologic specimen, or as a planned part of therapy in certain situations where there is an anticipated high risk of local– regional recurrence such as advanced oral cavity cancer. Systemic chemotherapy can also be given as primary treatment of FOP, high-risk cancers and in inoperable disease. Both chemoradiotherapy (CRT) and sequential therapy (ST), an approach that combines induction chemotherapy and CRT, are considered standard approaches for these settings.

postoperative chemoradiotherapy

Concurrent CRT has been proved to be an effective adjuvant in the postoperative setting. Two large randomized trials, one by the European Organisation for Research and Treatment of Cancer (EORTC 22931) and the other by the Radiation Therapy Oncology Group (RTOG) (RT 9501), have demonstrated that PO-CRT with bolus cisplatin delivered every 3 weeks with radiation therapy (BP-CRT) can significantly improve LRC in patients with poor prognostic risk factors [14–15]. The rate of distant metastases was minimally affected by PO-CRT. Importantly, survival was significantly improved in the EORTC study and survival improvement was of borderline significance in the RTOG study. The trials differed in the selection criteria for poor prognosis. A retrospective analysis pooled data from both trials and found extracapsular spread (ECS) and a positive surgical margin to be the major factors for which PO-CRT is beneficial [16]. The EORTC study also included perineural invasion, lymphovascular invasion and multiple involved lymph nodes as selection criteria; however, they appeared to be less important factors in the retrospective combined analysis. Long-term results indicated that survival differences lessened over time in both studies; however, these have not been published yet.

Incorporation of biologic therapies has also advanced. A randomized phase II trial from the RTOG (RTOG 0234), presented last year, reported the results of a comparison of weekly erbitux and weekly cisplatinum or docetaxel in patients with two or more positive lymph nodes, ECS or positive margins [17]. The study results were compared with the historic data from the RTOG 9501 study. Interestingly although both arms were somewhat better than historical data for LRC, a significant survival advantage for the weekly docetaxel/erbitux arm was reported, compared with historical controls and the weekly cisplatin/erbitux regimen. These early results indicated that the survival advantage for the docetaxel/erbitux arm resulted principally by a reduction in distant metastases. This was unexpected and unexplained. As a randomized phase II with only 200 patients in total and 2-year follow-up, the results cannot be seen as definitive yet.

Another early and intriguing trial delivered weekly chemotherapy with paclitaxel in the postoperative setting, followed by PO-CRT with cisplatin and paclitaxel in poor prognosis patients [18]. This study proved feasibility and indicated a benefit of early adjuvant treatment in the postoperative setting compared with the historical RTOG 9501 study results.

PO-CRT remains an area of promise and difficulty. Improvements in LRC have not always been accompanied by meaningful improvements in survival. Better pathologic selection criteria, new biomarkers and cessation of high-risk behavior, where appropriate, might improve outcomes. Data from ongoing trials with vascular targeting agents, alternative epidermal growth factor receptor (EGFR) inhibitors and new targeting agents such as mTOR, PI3K and c-MET inhibitors are becoming available.

concurrent CRT

Concurrent CRT is a standard of care for organ preservation and unresectable HNC. Studies and meta-analyses reported in the first decade of this century fully support the use of bolus cisplatin as a radiation sensitizer. The absolute improvement in survival has been small in meta-analysis and at 5 years is between 5% and 10% [19–20]. The contribution of CRT to LRC is larger and also significant. Little impact on distant metastases has been observed in randomized trials; hence much of the improvement in survival has resulted from improved LRC.

Organ preservation has remained an important goal in patient management. Even so, surprisingly, even the definition of organ preservation has been contentious among experts. In laryngeal and hypopharyngeal cancer organ preservation has been described variously as: (i) larynx preservation (LP)—no larynx surgery, (ii) laryngectomy-free survival (LFS)—alive with no laryngectomy and (iii) functional laryngectomy-free survival (FLFS)—alive with no laryngectomy, tracheostomy or stomach tube [21–22]. Careful definitions of end points determine success and interpretation of results. Many investigators would eliminate LP as less meaningful since it does not include survival, LRC or function. LFS does not include a functional assessment although survival is a key element of the measure. Even FLFS really does not fully take into account whether a patient is spared significant dysfunction, thus interpretation of studies can be difficult.

CRT has proved effective in laryngeal cancer for LFS. In the single randomized trial in North America, INT 91-11, BP-CRT significantly improved LFS compared with radiotherapy at 5 years, without a reduction in survival in patients with intermediate stage laryngeal cancer [6]. The improvement in LFS is associated with a significant improvement in LRC and a borderline impact on DM. The impact of BP-CRT on LFS was reduced by an increased incidence of deaths in the CRT arm, which appear to be late treatment effects (Table 1). Other organ preservation regimens have been tested in combined studies of laryngeal and hypopharyngeal cancers including alternating
CRT. At least one randomized phase III study (EORTC 24954) demonstrated that alternating platinum/fluorouracil–CRT (APF–CRT) and induction cisplatin/fluorouracil (PF) were equivalent for both FLFS and survival [8]. This study used a lower dose of radiotherapy in the CRT arm than is generally delivered today in CRT treatments. Notably however, treatment-related and non-primary cancer deaths were minimal in the CRT arm with the reduced dose of radiation (Table 1). Based on this randomized trial, patients with laryngeal and hypopharyngeal cancer can also be treated with either PF induction chemotherapy or APF–CRT for organ preservation.

CRT for advanced disease has been proved to be an effective treatment, with well-documented evidence of a survival improvement from randomized trials. Treatment with platinum-based therapy has been shown by meta-analysis to be the most efficacious therapy option. BP-CRT has been evaluated extensively in the USA. The rationale for BP-CRT is based on the ground-breaking work by the Wayne State Head and Neck oncology group [23]. They demonstrated in a phase II trial of salvage CRT that treatment with post-induction BP-CRT was feasible, and, most importantly, improved local control, leading to survival in a meaningful fraction of patients who had failed induction PF. Patients who fail to respond or progress during PF induction chemotherapy have extremely poor LRC and survival when treated with radiation only. This phase II trial clinically demonstrated that there is direct, non-cross-resistant, activity of cisplatin as a radiation sensitizer in HNC and was the foundation for future CRT trials in the USA. The Intergroup trial for unresectable disease subsequently and firmly demonstrated that 3-year survival was significantly improved in patients treated with BP-CRT [24]. As with other CRT trials, the survival improvement was the result of improved LRC. Minimal effects were observed in this trial on the incidence of DM. Also, as with other CRT trials in that time period, a substantial number of non-cancer deaths occurred. Thus, increased toxicity and mortality in the CRT arm has been a price for improved LRC and survival.

Carboplatinum and fluorouracil (CF) for concurrent therapy (CF-CRT) has also been investigated in randomized trials for locally advanced HNC [25–26]. While carboplatinum is as good a radiation sensitizer as cisplatinum, its direct antitumor activity is less [27]. Thus, carboplatin has less systemic activity than cisplatin. Carboplatin is much better tolerated with respect to nausea, vomiting and renal function than cisplatin. These are important toxic effects in patients receiving head and neck radiotherapy, hence carboplatin can be given more consistently throughout treatment compared with BP. In two trials in advanced HNC completed in Europe, CF demonstrated significant impact on survival. The results of the GORTEC and Staar trials were positive in oropharynx for survival with CP, with the impact again limited to LRC and minimal effects on DM. As with other reports, morbidity and mortality with CRT were increased.

One potentially significant advance in CRT has been the combination of radiotherapy with erbitux. CRT with erbitux, an anti-EGFR antibody, has proved effective in a single randomized trial for locally advanced HNC [28]. This trial was recently updated with a median follow-up of 5 years and demonstrated a significant improvement in LRC and in survival in patients receiving erbitux as a single agent with CRT. A randomized phase III trial comparing BP-CRT and BP-CRT plus erbitux (BPE-CRT) has recently completed accrual and is awaiting analysis. Results from this trial are eagerly awaited.

There have been many platinum-based phase II CRT trials reported over the past decade. Several notable ones deserve attention. A randomized phase II trial completed by RTOG (RTOG 9703) and reported in 2004 compared three chemotherapy regimens for CRT: weekly cisplatin and paclitaxel (WPP); hydroxyurea, fluorouracil (HFX) and a late PF therapy boost [29]. Data indicated excellent survival in the HFX and WPP arms. Both treatments were well tolerated. Although no further phase III studies have been initiated, these therapies are of considerable interest and have supported other phase II studies. Weekly carboplatinum/paclitaxel CRT (CP-CRT) has been studied in several phase II trials [30–31]. This regimen has been well tolerated with excellent survival results. The addition of paclitaxel to carboplatinum or cisplatinum in weekly therapy with CRT has great appeal because of the synergy between these drugs and the significant radiation-sensitizing properties of the taxanes. Combinations of taxanes, taxanes and EGFR inhibitors have also been studied in a variety of settings and perhaps represent the next stage of aggressive treatment for CRT. Several phase II studies with excellent results have been reported [32]. Although not commonly used outside of a few centers, HFX-based therapies have been well studied and reports of trials incorporating taxanes and platinum in this CRT backbone with good and interesting results have been published [33–36]. Because of the continued high rate of local–regional failure in patients with advanced disease it is possible that multiple sensitizers, as studied in these trials may improve LRC over single agents. Such combinations may also have additional efficacy against systemic disease.

<table>
<thead>
<tr>
<th>End point population</th>
<th>Therapyab</th>
<th>Survival (%)b</th>
<th>LRC</th>
<th>LFS</th>
<th>Non-primary cancer deathsb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor 1996</td>
<td>Unresectable, survival</td>
<td>PF versus PF-CRT</td>
<td>28 versus 26</td>
<td>45 versus 51</td>
<td>NR versus 13 versus 28</td>
</tr>
<tr>
<td>Int 91-11 2006</td>
<td>Larynx, LFS</td>
<td>PF versus BP-CRT</td>
<td>59 versus 54</td>
<td>55 versus 69</td>
<td>45 versus 47 versus 28 versus 39</td>
</tr>
<tr>
<td>EORTC 24954, 2009</td>
<td>Larynx/hypopharynx, LFS</td>
<td>PF versus APF–CRT</td>
<td>49 versus 52</td>
<td>68 versus 67</td>
<td>31 versus 36 versus 29 versus 26</td>
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*aBP, bolus cisplatin.
*bAll data are based on 5-year follow-up when available.

Table 1. Randomized trials comparing induction PF with CRT
**Table 2.** Results of phase III trials comparing OS, progression-free survival (PFS) and organ preservation for TPF and PF in curable patients

<table>
<thead>
<tr>
<th>Study population</th>
<th>N</th>
<th>Primary end point</th>
<th>Regimen</th>
<th>Significant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tax 323 inoperable [42]</td>
<td>358</td>
<td>PFS</td>
<td>PF/RT versus TPF/RT</td>
<td>TPF better, PFS and OS $P &lt; 0.01$</td>
</tr>
<tr>
<td>TAX 324 locally advanced [5, 43]</td>
<td>503</td>
<td>OS</td>
<td>PF/CRT versus TPF/CRT</td>
<td>TPF better, 5-year PFS and OS $P = 0.01$; LFS $P &lt; 0.03$</td>
</tr>
<tr>
<td>GORTEC 2000-01 resectable larynx/hypopharynx [9]</td>
<td>213</td>
<td>Larynx preservation (LP/FLFS)</td>
<td>PF/RT versus TPF/RT</td>
<td>TPF better, LP/FLFS $P &lt; 0.04$</td>
</tr>
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**sequential therapy**

ST represents a synthesis of induction chemotherapy and CRT. PF-based induction chemotherapy proved effective in improving survival by improving LRC and distant metastases in patients with locally advanced HNC [37–38]. Significant improvements in survival and organ preservation were reported in randomized trials comparing PF with radiotherapy, radiotherapy and surgery, or as a substitute for surgery [7]. CRT and PF induction therapy were found to be equivalent when compared in three randomized trials (Table 1) [6, 8, 39]. Differences in outcome between PF and BP-CRT or PF-CRT were seen primarily as a result of the increased mortality associated with CRT and decreased LRC observed with PF. Hence survival and local–regional (organ preservation) end points proved to be equal between the two paradigms of therapy. Early phase II studies of ST using PF-based regimens indicated that an improvement in outcome might be achievable [40–41]. However at the same time as these early sequential experiments, taxanes became available. The excellent single-agent activity of taxanes has resulted in an increased interest in induction therapy and resulted in three phase III trials of taxotere combined with PF (TPF) [5, 9, 42]. All three randomized TPF trials demonstrated a significant 30% improvement in survival or organ preservation with less toxicity when TPF was compared with PF (Table 2). One of these trials, TAX 324 was a sequential trial comparing TPF with PF, both followed by carboplatinum-based CRT. TPF has become a standard of therapy for patients with locally advanced HNC for both unresectable patients and organ preservation.

Based on an analysis of outcomes from induction and CRT trials it makes very good biologic sense to combine induction chemotherapy with CRT and surgery in a ST paradigm. In a ST treatment plan, such as TPF in TAX 324, systemic induction therapy may better prepare the local and regional area for subsequent therapy by reducing tumor bulk, normalizing vasculature and improving local function while reducing risk of distant metastases and local failure [5, 10, 43]. The immediate period after induction chemotherapy is biologically critical for tumor control. Tumor cells in the primary site and regional tissues are thought to begin rapid proliferation if they have survived in the period immediately after therapy and may also have acquired partial resistance to therapy. Giving non-cross-resistant therapy with radiation and chemotherapy with minimal delay should improve LRC as predicted by the outcomes in the Wayne State study.

Several sequential phase II trials have been reported. The University of Pennsylvania reported a sequential program trial that included two cycles of very-high-dose carboplatinum and paclitaxel followed by single-agent weekly CRT with paclitaxel [44]. Survival was >60% at 3 years. The University of Chicago used an induction regimen of 6 weekly cycles of intensive carboplatinum/paclitaxel (CP) chemotherapy followed by aggressive split course CRT with paclitaxel, hydroxyurea, 5-fluorouracil, and XRT [36]. The 3-year overall survival rate in this phase II study was 70%. The original Chicago induction regimen of weekly carboplatinum and paclitaxel has been modified by ECOG and MD Anderson by the addition of weekly Cetuximab in phase II trials [45–46]. After induction therapy, patients are treated with CRT with weekly carboplatinum, paclitaxel and Cetuximab. In the ECOG trial there is a provision to perform surgery midway through radiotherapy if there is persistent disease based on an interim positive biopsy. The Minnie Pearl Cancer Research Network Trial carried out a study of high-dose CP for two cycles with 6-week continuous infusion of 5-fluorouracil [47]. This induction regimen was followed by CP weekly with radiotherapy. There was a 51% 3-year survival in this very advanced group of patients. ECOG reported a trial similar to the UP trial with a 76% 2-year survival also using high-dose CP [48]. In the ECOG trial docetaxel was given weekly with XRT. The ECOG trial stratified patients with laryngeal and oropharyngeal cancer and explored the efficacy of therapy in HPV-related oropharyngeal cancer (HPVOPC). Their data showed an enormous survival advantage for patients with HPVOPC [49]. Another ECOG trial explored treating patients with docetaxel/cisplatin/cetuximab followed by weekly cisplatin/cetuximab CRT and cetuximab maintenance.

The University of Michigan has taken a dramatically different approach. They have used induction chemotherapy to select patients for organ preservation or surgery. The initial response to one cycle of induction therapy is used to predict local–regional failure by radiotherapy [11]. Responders to one cycle of PF received immediate CRT with bolus cisplatin followed by adjuvant paclitaxel. Non-responders to one cycle received surgery. Survival and organ preservation rates are excellent in this population of resectable oropharyngeal cancer patients. This population is not directly comparable to the more advanced patients treated in other sequential studies. However, in the light of the older Wayne State study and with the newly reported results from TAX 324 and the GORTEC trial demonstrating that TPF improves LRC and organ preservation,
it seems that a complete course of full-dose induction therapy followed by CRT might be more effective in organ preservation. Because of the success of TPF induction therapies, there are now several phase III trials that compare CRT with TPF-based ST. The University of Chicago has completed a phase III trial comparing DHFX CRT and ST with TPF plus DHFX. An Italian Trial comparing TPF followed by PF-CRT with PF-CRT is nearing completion. A Spanish trial comparing three arms, TPF or PF plus cisplatinum-based CRT with CRT alone was recently reported with very preliminary data. Finally, the Paradigm Trial comparing TPF followed by carboplatinum with cisplatinum plus aggressive radiotherapy was closed early because of slow accrual. These studies will have final data in 2–3 years and will help define treatment for the next series of studies.

the future

The next decade will bring new and exciting developments in the treatment of locally advanced HNC. The HPV epidemic will change the nature of HNC throughout Europe and the USA. This separation of HNC into two distinct diseases is important. HPV disease responds well to therapy; however, the best treatments are yet to be determined. The challenges of the next decade will include understanding risk factors, molecular biomarkers and treatment selection to inform treatment selection. Can we change therapy to improve survival and reduce toxicity in the HPV patients? can we identify new treatments to improve outcomes in patients with environmentally related cancers? and how can we integrate surgery, radiotherapy and chemotherapy to achieve these outcomes?

disclosures

Dr Posner has indicated that he has received honoraria from Sanofi Aventis and Millennium Pharmaceuticals. He has conducted clinical research for Abraxis, Sanofi Aventis, Astra Zeneca, Bristol Myers Squibb, Amgen, NCI, NIAID, Imclone, Novartis and Actogenix. He has acted as a consultant to Amgen, GlaxoSmithKine, Sanofi Aventis, Bristol Myers Squibb, NCI, OxiGene, Imclone, Novartis, Merck, EMD Serono, Onc-Q-ity, Pfizer and Oncolytics.

references


