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Docetaxel, Cisplatin, 5-Fluorouracil (TPF)-Based Induction Chemotherapy for Head and Neck Cancer and the Case for Sequential, Combined-Modality Treatment

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ABSTRACT

Since the publication of the Veterans Affairs study in the early 1990s, much has been learned regarding the role of chemotherapy, radiation therapy, and more importantly, the role of combined-modality treatment with chemoradiation in the therapy of locally advanced head and neck cancer. There continues to be widespread variation and controversy in the timing, schedule, and intensity of chemotherapy and chemoradiation. Herein, we present the various approaches currently used in the year 2003 with a specific emphasis on the role of sequential combined-modality therapy combining chemotherapy, chemoradiotherapy, and surgery in the treatment of these malignancies. ***The Oncologist*** *2003;8:35-44*

INTRODUCTION

The treatment of locally advanced squamous cell cancer of the head and neck (SCCHN) remains contentious and controversial. Opinions about the proper role and timing of chemotherapy continue to be divided among experts in the field. There is little disagreement among oncologists that for advanced, stage IV disease chemotherapy should be an integrated component of curative therapy [1, 2]. The difficulties lie in the timing of therapy and in the biological models that are used to predict the best treatment. The place of chemotherapy in intermediate-stage disease is less secure. Much of this disagreement can be traced to the great heterogeneity in biology, prognosis, staging, and response of SCCHN originating from different sites as well as the heterogeneity in populations included in nonrandomized and randomized trials. In addition, chemotherapy can be delivered in a variety of plans, including induction chemotherapy, chemoradiotherapy, or as a sequential treatment plan combining induction chemotherapy with chemoradiotherapy regimens.

INDUCTION CHEMOTHERAPY

Cisplatin/5-fluorouracil (PF)-based induction chemotherapy is highly active in SCCHN (Table 1) [3-6]. Despite a disposition in the literature to the contrary, randomized trials and meta-analyses have shown that full-dose PF, as opposed to other induction regimens, significantly improves survival in patients with locally advanced SCCHN [4, 5, 7, 8]. The most recent, complete, and technically sophisticated meta-analysis specifically reported that PF chemotherapy resulted in a significant 16% lower risk of death in curatively treated SCCHN patients compared with controls. This improvement was only true for PF induction regimens. In that meta-analysis, PF chemotherapy was associated with a

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Table 1. Selected studies of PF induction chemotherapy

Investigators	*n* of patients	Induction chemotherapy	Local therapy	Comments
Veterans Affairs [6]	332	PF × 3	S/XRT versus XRT	64% larynx preservation with chemotherapy; fewer distant metastases
European Organization for the Research and Treatment of Cancer [3]	194	PF × 3	S/XRT versus XRT	42% larynx preservation with chemotherapy
Paccagnella et al. [5]	237	PF × 4	S/XRT versus XRT	Survival advantage for chemotherapy in subgroup analysis
Domenge et al. [4]	174	PF × 3	S/XRT versus XRT	Survival advantage for chemotherapy

Abbreviations: S = surgery; XRT = radiation therapy.

significant ($p < 0.01$) 5% absolute improvement in 5-year survival over the control treatment, a survival improvement that is very close to the 8% improvement observed in the subset of chemoradiotherapy trials [7, 9]. It is notable that other combinations, including platinum-containing polychemotherapy regimens, did not achieve a significant level of survival improvement.

Two large, well-run and aggressive European PF-based trials, published after the cutoff dates for the meta-analyses, also demonstrated significant, long-term survival improvements in patients treated with induction chemotherapy. In both trials, patients were stratified at entry into resectable and unresectable disease. After induction chemotherapy, initially resectable patients underwent surgery and then radiotherapy, while unresectable patients received definitive radiotherapy. In both trials, full-dose PF induction chemotherapy resulted in a significant improvement in survival in patients with unresectable locally advanced SCCHN compared with radiotherapy alone [4, 5]. In the Gruppo di Studio trial [5], there was no improvement in the survival of the resectable patients receiving chemotherapy, while unresectable patients had a significant, twofold improvement in survival. The surgical patients were resected immediately after induction chemotherapy and then irradiated. Rather than suggesting that induction chemotherapy was ineffective in this setting, as some have done, it could be argued that surgery, timed to occur in resectable patients between chemotherapy and postoperative radiotherapy, negatively affected the impact of the induction chemotherapy [5]. As we now know from studies in radiation biology, there may be a higher risk of tumor repopulation by residual tumor cells and expansion of resistant cell populations when radiotherapy to the region is delayed or interrupted. In addition, radiation doses and fields may have been less intense in the postoperative setting. Certainly, organ preservation is nonexistent in this study group. In comparison, the unresectable patients had postirradiation resection of nodal disease if their postirradiation primary site biopsies were negative. Surgery in this setting may have been more properly timed and aimed at areas of bulky disease where resistant cells may have been expected to persist.

In the Groupe d'Étude des Tumeurs de la Tête et du Cou trial, there was a significant and sustained improvement in survival in both resectable and unresectable populations receiving induction chemotherapy [4]. It should be noted though that an improvement in outcomes in the surgically resectable population could be achieved in the future and could be the result of changes in surgical timing, radiation dose, newer techniques, a better medically fit population, and/or attention to rapid initiation of radiotherapy.

PF-based induction chemotherapy also has been effective in replacing surgery for organ preservation in the larynx and the hypopharynx and has altered the standard therapeutic approach to intermediate- and advanced-stage disease in these sites [3, 6]. Although functional organ preservation with induction chemotherapy represents a major advance in treatment of these sites and has been extrapolated to oropharyngeal sites in practice, survival has not been improved in resectable patients when PF-based induction therapy replaced surgery. This is the case even though survival in unresectable patients has been significantly improved by this approach [4, 5]. It is important to note that, in the organ preservation trials, the patients had resectable disease, and a majority of those patients had stage III disease, with limited involvement of regional lymph nodes and relatively small (T1-T3) primary tumors. One can speculate that more advanced cases (patients with large T3, T4, N2, or N3 disease) may well have benefited more from induction therapy than those with smaller disease volumes and less risk of recurrence or metastases.

Even with a significant survival improvement with PF-based induction chemotherapy in unresectable patients, absolute survival and disease-free survival remain less than

50%. Clearly, there is a substantial need for improvements in therapy for intermediate- and advanced-stage patients. In randomized induction trials, response rates to PF ranged from 60%-80%, and clinical complete response rates were more modest in a range of 20%-30%. The quality of response is dependent on the volume of disease. Patients with advanced nodal presentations have particularly poor responses and survival and, as noted above, are excluded from many organ preservation trials [3, 6, 9]. Considerable efforts have been devoted to improve on PF-based induction chemotherapy.

The taxanes have been proven to have significant single-agent activity in SCCHN. Many regimens have been developed to try to take advantage of the activity of paclitaxel and docetaxel. Phase II trials of high-dose paclitaxel and carboplatin, reported by *Dunphy et al*., have shown promising activity [10]. A more aggressive, multiday regimen that added ifosfamide (TIC) has also been reported with considerable success in a phase II trial, but additional toxicity and a complicated therapy may outweigh marginally different response rates afforded by the addition of ifosfamide [11]. The use of carboplatin with paclitaxel takes advantage of the lower neurotoxicity of carboplatin compared with cisplatin and permits high-dose combinations and even weekly combination treatments with paclitaxel, which is neurotoxic. Carboplatin is less nephrotoxic, neurotoxic, and emetogenic than cisplatin and may improve the toxicity profile of paclitaxel. In platinum-based combinations for SCCHN, however, carboplatin is less effective than cisplatin both in the curative and palliative settings [12, 13]. It is possible, however, that the toxicity advantages of carboplatin combined with paclitaxel may be sufficient to outweigh the documented response advantage of cisplatin in the curative setting, although a phase III trial has not been performed.

We [14-17] and others [18] have explored adding docetaxel to PF-based chemotherapy to improve the response rates of PF induction therapy [14-17]. This was partially based on previous experience accumulated with the use of PF and leucovorin (PFL) as an induction regimen [19, 20]. The major dose-limiting toxicity of docetaxel is myelotoxicity, which can be controlled with antibiotic support. We completed four phase II studies of docetaxel- and PF-based chemotherapy (Tables 2 and 3). These studies included 130 patients treated and followed for a minimum of 3 years. Data are available on long-term survival (130 patients) and sites of failure (101 Dana Farber Cancer Institute [DFCI] patients) [14-17, 21]. The 101 DFCI patients were treated in a uniform manner. After three cycles of induction chemotherapy, they received hyperfractionated (HFX) radiotherapy and then surgery for advanced and partially responsive nodal disease. The demographics of patients in the trials and survival data are presented in Table 2. The docetaxel, cisplatin, 5-fluorouracil (TPF) trial was performed as a multicenter trial, with simplified dosing compared with the first three high-dose trials. The high-dose trials required growth factor support and were associated with substantial toxicity, which included grade 4 neutropenia, severe mucositis, nausea, vomiting, and fatigue. The majority of patients in all trials had advanced nodal disease. As shown in Table 2, response rates, complete response rates, and 3-year survival data from all four trials are excellent.

An analysis of failure for the 101 patients treated at the DFCI is shown in Table 3. There were 36 disease failures (36%) among 101 treated patients. There were 25 (25%) local-regional (LR) failures, and five patients (5%) with distant metastases (DM) and LR failure, while six patients (6%) had DM as their only site of failure. The overall rate of DM was 11%. There were only eight (8%) relapses after 2 years. At the time of writing of this paper, 67% of patients were

Table 2. Docetaxel- and PF-based induction trials

	TPFL5	TPFL4	Op-TPFL	TPF	Total
n of patients	23	30	34	43	130
Follow-up, months (median)	65-90 (73)	51-64 (57)	36-53 (44)	41-48 (44)	36-90 (48)
Oropharynx	47%	30%	41%	43%	43%
N2 + N3	76%	54%	76%	57%	67%
Complete response	61%	63%	44%	42%	50%
Partial response	39%	30%	50%	51%	36%
1-year OS	100%	83%	82%	98%	91%
2-year OS	83%	80%	68%	79%	77%
3-year OS	78%	77%	62%	77%	73%

Abbreviations: TPFL = docetaxel + cisplatin + 5-fluorouracil + leucovorin; Op = outpatient; OS = overall survival.

Table 3. An analysis of failure for TPF-based trials*

	TPFL5	TPFL4	Op-TPFL	TPF	Total
n of patients	23	30	34	14	101
LR failure only	4	10	10	1	25
LR failure + DM	1	3	1	0	5
Total LR failures	5	13	11	1	30
DM only	1	3	2	0	6
Total DM	2	6	3	0	11
Total failures	6	17	11	2	36
Relapse after 2 years	2	5	1	0	8

*Dana Farber Cancer Institute patients, minimum follow-up was 3 years.
Abbreviation: Op = outpatient.

alive. The excellent 3-year survival rates suggest that TPF-based regimens could lead to an improvement over PF regimens; however, as with PF induction therapy, local-regional failure remains the major problem [21].

The phase II data for TPF-based induction chemotherapy support the notion that docetaxel can improve on the results of PF induction chemotherapy. The data on survival for the more simplified TPF regimen are comparable with those achieved with aggressive high-dose regimens. However, local-regional recurrences remain the principal cause of failure. This observation, which pervades all phase II and randomized phase III induction therapy trials, suggests that local-regional dose intensity needs to be increased in patients with advanced disease treated with induction chemotherapy.

Chemoradiotherapy

Chemoradiotherapy increases local-regional dose intensity. The notion that dose intensity is important for local-regional control relates to the biological observation that SCCHN may be a relatively local-regional disease compared with other cancers of the upper aerodigestive tract. Despite aggressive local-regional surgery and/or radiotherapy, the majority of patients with curable intermediate or locally advanced disease will die from local-regional persistence or recurrence. Chemotherapy combined with radiotherapy can increase local-regional dose intensity by either sensitizing cancer cells to radiotherapy, independently killing tumor cells, or through some combination of both mechanisms. Some agents, such as hydroxyurea, work only through radiation sensitization, whereas taxanes work independently by both mechanisms—sensitization and direct tumor cell killing. Thus, docetaxel and paclitaxel can promote radiation sensitization by mechanisms that are independent of their direct antitumor activity [22-24]. Unfortunately, these two agents promote a significant normal tissue sensitization to radiotherapy as well, and chemoradiotherapy with taxanes is associated with a brisker local reaction than radiotherapy alone [25, 26]. Cisplatin and carboplatin appear to be equally good radiation sensitizers, but they may be less effective than the taxanes [27, 28]. On the other hand, platinums mediate significantly less normal tissue radiation damage than taxanes. It should be noted, though, that most of the data showing benefit from chemoradiation are derived from single-agent cisplatin or platinum combinations.

Chemoradiotherapy can be delivered in a number of different formats. For example, chemotherapy can be given as a single agent or as combination therapy in a cycle every 3 weeks, weekly, continuously, or even at the end of a course of radiotherapy. Split-course therapies give radiotherapy and chemotherapy simultaneously with breaks for recovery, or in an alternating sequence. When chemotherapy is being used to provide both local-regional sensitization and systemic therapy, more aggressive dosing in cycles may make biologic sense. Treatments such as bolus cisplatin or carboplatin plus 5-fluorouracil every 3 weeks are examples of this compromise in targeting the biologic effect to both the local-regional disease and the potential distant metastases. Because of local and systemic side effects, the chemotherapy is moderated to avoid interfering with radiotherapy. When the risk of distant metastases is more limited, weekly single-agent therapy or continuous therapy may provide more local and regional sensitization, although for certain combinations and single agents, weekly therapy may be as systemically effective as larger doses given every 3 to 4 weeks. Here, total dose may be more important for systemic control while local sensitization may be promoted by weekly dosing.

Unfortunately, the potential biologic implications of different schedules have led to a plethora of different chemoradiotherapy regimens that have shown considerable differences in scheduling and drug choice [29-34]. As a result, chemoradiotherapy regimens have shown both significant and nonsignificant improvements in survival and local-regional control compared with standard radiotherapy in patients with resectable and unresectable disease (Table 4) [29, 30-34, 36]. Randomized trials have demonstrated that a regimen of high-dose single-agent cisplatin, given every 3 weeks with radiation therapy was significantly better than once-daily fractionated radiation for unresectable disease and nasopharyngeal cancer (NPC). The Intergroup studied this regimen (INT-026) and demonstrated a significant improvement in survival in patients with unresectable disease treated with bolus cisplatin chemoradiotherapy compared with once-daily radiotherapy [36]. In NPC, an identical chemoradiotherapy regimen followed by adjuvant PF significantly improved survival in patients compared with radiotherapy alone [33].

A combination therapy regimen of carboplatin and 5-fluorouracil, delivered over 4 days, twice during a course of once-daily radiation therapy resulted in significantly better overall survival rates in patients with resectable and unresectable oropharyngeal cancer. In that study, by *Calais et al*., 2-year survival was greater at 51% (compared with 31%) with the addition of chemotherapy to a standard radiotherapy program [29]. A phase III comparison of cisplatin/5-fluorouracil therapy during HFX radiotherapy compared with HFX radiotherapy alone did not demonstrate a significant difference in absolute survival, although a nonsignificant improvement was observed in the chemoradiotherapy arm [30]. A phase III trial of a carboplatin/5-fluorouracil regimen, similar to the *Calais et al*. regimen, with concomitant boost radiotherapy in advanced oropharynx and hypopharynx patients also failed to show a significant difference between the radiotherapy and the chemoradiotherapy regimens [34]. Despite the lack of an overall survival difference, the 1- and 2-year survival rates with local control favored the chemoradiation arm, and the subset of oropharyngeal patients had a significantly better survival with chemoradiotherapy than with radiotherapy alone. It is also noteworthy that this study reported that 25% of the radiotherapy patients that survived 2 years were percutaneous endoscopic gastrostromy (PEG) dependent, and 50% of the chemoradiotherapy patients were also PEG dependent. These later data suggest that: A) site may be important in assessing treatments; B) the absolute survival value of chemoradiotherapy may not be as great when patients are treated with concomitant boost therapy, and C) the late local and long-term toxicities of both chemoradiotherapy and HFX radiotherapy are significant.

A number of phase I/II and small phase III trials of chemoradiotherapy regimens have had excellent results. Weekly single-agent carboplatin was tolerable and active [37]. A randomized trial of daily radiotherapy either alone or with daily cisplatin or carboplatin demonstrated a significant survival advantage for both cisplatin and carboplatin compared with radiotherapy alone, but patient numbers were very small [28]. A later study confirmed that daily cisplatin improved survival over HFX radiotherapy alone [38]. A University of Maryland study reported a 48% 3-year survival rate with a regimen of weekly carboplatin and paclitaxel during once-daily radiotherapy [39]. This regimen is currently used extensively in community practice and provides total doses of carboplatin and paclitaxel that are equivalent to two full cycles of bolus therapy. The ease of administration and toxicity profile make this regimen appealing. In a three-arm randomized phase II trial (97-03), the Radiation Therapy Oncology Group (RTOG) evaluated three regimens: weekly cisplatin plus paclitaxel; concomitant boost chemoradiotherapy with cisplatin and 5-fluorouracil continuously for the last 2 weeks of once-daily radiotherapy, and the HFX regimen of hydroxyurea plus 5-fluorouracil [40]. This trial resulted in 2-year survival

Table 4. Randomized trials comparing definitive radiotherapy with concurrent chemoradiotherapy

Study	*n* of patients	Overall survival (%)			Local-regional control (%)			Disease-free survival (%)		
		RT	CRT	*p*	RT	CRT	*p*	RT	CRT	*p*
Calais et al. [29]	226	31	51	0.02	42	66	0.03	20	42	0.04
Brizel et al. [30]	116	34	55	0.07	44	70	0.01	41	61	0.08
Smid et al. [31]	49	—	—		—	—		9	48	0.001
Staar et al. [34]	240	39	48	0.09	45	51	0.14	—	—	
Adelstein et al. [32]	100	48	50	0.55	45	77	<0.001	51	62	<0.001
Al-Sarraf et al. [33]	147	47	78	0.005	—	—		24	69	<0.001
Adelstein et al. [36]	184	20	36	<0.05	—	—		34	56	<0.05

Abbreviations: RT = radiotherapy; CRT = chemoradiotherapy.

rates of 60%-67% in all three arms, and although the toxicity was considerable, the RTOG concluded that these treatments may be better than single-agent cisplatin. Surprisingly, the RTOG chose not to evaluate any of these regimens in phase III against single-agent cisplatin. The University of Chicago has reported a long experience with split-course chemoradiotherapy regimens, the most recent of which, THFX, was associated with a high rate of local-regional control [41]. This intensive regimen resulted in a 60% 3-year survival rate in a very advanced population of treated patients but was associated with considerable local toxicity and hospitalization throughout treatment.

Distant failures and second primary cancers have proven to be increasing causes of failure and death in patients with locally advanced SCCHN treated with chemoradiotherapy, particularly in patients with large bulky tumors or larger neck presentations [9, 35, 42]. As local-regional control has improved, more patients are surviving longer, and this has allowed distant metastases to develop, contributing to late mortality. Also, importantly, chemoradiotherapy programs, particularly intensive regimens, are associated with considerable long-term morbidity and dysfunction, much of which has gone under-reported or unrecognized in earlier clinical trials where this mortality may have been reported as non-cancer-related deaths [30, 34, 41]. These long-term morbidities are particularly important if patients are surviving their disease longer and where considerable differences in the morbidity of regimens may be expected. This is particularly important when there are small differences in survival among regimens that vary significantly in long-term toxicity and dysfunction.

The two therapies that may be considered “standard” are the high-dose, bolus cisplatin therapy and the *Calais et al*. regimen, although confirmatory trials have not been reported [29, 33, 36]. Both have shown improved survival over once-daily radiotherapy, and both have limited morbidity. Although concomitant boost radiotherapy is considered a standard versus once-daily radiotherapy, there was no significant difference in survival with accelerated treatments compared with once-daily radiotherapy [43]. The RTOG is currently comparing three cisplatin boluses and once-daily radiotherapy with two boluses with concomitant boost radiotherapy to address the issue of schedule.

Recently, the Intergroup larynx preservation trial (91-11) was reported in abstract [44]. This phase III trial compared PF induction chemotherapy, chemoradiotherapy with bolus cisplatin, and once-daily radiotherapy for patients with larynx cancer. Surgery was reserved for salvage therapy. The trial accrued a population of patients with the same tumor characteristics as that entered in the Veterans Affairs (VA) larynx trial. Patients had predominantly stage III, low-volume disease, with limited nodal disease and limited-stage primary tumors. In this intermediate prognosis group of patients, preliminary data suggest that larynx preservation was better with chemoradiotherapy. Most outcome differences among the three arms were nonsignificant except that laryngectomy-free survival was highest in the chemoradiotherapy arm. Both chemotherapy arms also significantly reduced the incidence of distant metastases. The final report of this study is pending, and the results as reported may change; however, the data are highly suggestive that, in intermediate-stage disease, chemoradiotherapy may be better than radiotherapy alone for larynx preservation, but the data do not extrapolate to advanced disease.

Aside from this single trial, there are no large, adequately powered phase III trials in advanced SCCHN comparing full-dose PF induction chemotherapy of three or four cycles with chemoradiotherapy. We can extrapolate, however, that both chemoradiotherapy and induction chemotherapy have advantages and disadvantages. Both are associated with a significantly greater rate of survival in advanced disease and with organ preservation compared with surgery. Chemoradiotherapy is associated with more significant local morbidity, which may be aggravated by incorporating 5-fluorouracil, a taxane, or HFX radiotherapy into the treatment [25, 26, 34, 42]. Chemoradiotherapy is associated with greater local-regional dose intensity, lower local-regional recurrence, and a higher risk of distant failure, and induction chemotherapy is associated with fewer distant metastases but inadequate local-regional control. Induction chemotherapy may also improve functional outcome by reducing tumor burden prior to radiotherapy and reducing the potential for scarring. This may be particularly important for large primary tumors and neck disease. Notably, induction chemotherapy is associated with high clinical and pathologic complete response rates, and complete response is predictive of local-regional control [45]. Assessment of primary site and nodal response can permit an adjustment in the intensity of subsequent chemoradiotherapy. For example, nonresponders might receive more intensive multiagent chemoradiotherapy than complete responders.

Sequential Therapy

It appears then that the curative treatment of advanced disease could be best effected by combining the best induction chemotherapy with chemoradiotherapy in an integrated program. Combining induction chemotherapy with chemoradiotherapy in a sequential treatment plan, based on differences in activity and toxicity of each paradigm, could improve outcomes. In sequential treatment, induction chemotherapy followed by chemoradiotherapy followed by selected surgery to sites of bulk disease or for salvage may optimize therapy [46, 47]. In addition, as sequential treatment plans develop, postinduction chemoradiotherapy can be intensity adjusted based on response to induction chemotherapy and prognostic factors.

Several such sequential treatment plans have been investigated in phase II/III trials (Table 5) [1, 48-52]. Investigators at the University of Pennsylvania recently reported their results using an induction regimen of high-dose carboplatin and paclitaxel (CP) delivered with G-CSF for two cycles [50]. This was followed by moderate-dose, weekly chemoradiotherapy with paclitaxel. Patients with large neck nodes underwent surgery and then two additional cycles of CP chemotherapy. This is, patently, very intensive treatment. Current data suggest a 3-year survival rate of 70%, but with a median follow-up of only 31 months. The complete response rate to induction chemotherapy was a low 13%, which is a direct result of giving two rather than three cycles of induction therapy. *Vokes et al.* and *Gray et al.* reported additional CP-based induction regimens in abstract form [49, 51]. The University of Chicago group [49] gave CP chemotherapy weekly for 6 weeks, followed by THFX chemoradiotherapy. The Minnie Pearl Cancer Research Network trial used high-dose CP for two cycles with 6 weeks of continuous infusion 5-fluorouracil followed by CP weekly with radiotherapy [51]. Both of those trials reported high hospitalization rates during chemoradiotherapy but good short-term results. The Eastern Cooperative Oncology Group (ECOG) recently completed a trial similar to the CP trial (ECOG 2399) without the adjuvant component; however, no data are available for that study.

Researchers at the University of Michigan have chosen to use induction chemotherapy to select patients for organ preservation or surgery [52]. After one cycle of PF induction chemotherapy, patients are assessed for response, and then, nonresponders undergo laryngectomy. Responders receive chemoradiotherapy with bolus cisplatin. Surgery is then applied to patients with persistent disease, and two cycles of adjuvant paclitaxel are given to complete responders. Data from this study are forthcoming.

Most of these trials approach sequential therapy from the point of view that the induction treatment should be minimized to an adjuvant role. This may not be optimal. Data from the VA larynx trial suggest that it is difficult to assess response in the larynx clinically, and this is also true of other sites in the head and neck. In addition, clinical data suggest that assessment of a partial response is not accurate after one cycle, and the optimal number of cycles to obtain an assessment of complete response is three or four cycles of platinum-based induction therapy [53]. In addition, in comparison with chemoradiotherapy regimens, the morbidity of induction chemotherapy is transient and controllable. To optimize the integration of induction chemotherapy and chemoradiotherapy for survival and morbidity, it may be necessary to give more aggressive induction therapy by giving at least the equivalent of three cycles of high-dose treatment. Furthermore, in the curative setting, cisplatin may be preferred in the induction phase of therapy.

We have initiated a multicenter, randomized, phase III trial comparing a sequential treatment plan of TPF versus PF induction therapy, followed by chemoradiotherapy with weekly carboplatin [1]. This phase III trial is currently ongoing and has accrued over 400 patients.

Table 5. Sequential chemoradiotherapy trials

Trials	Induction chemotherapy	Concomitant chemoradiation	Adjuvant chemotherapy	Surgery
TAX 324, phase III	PF/TPF every 3 weeks × 3	Weekly carboplatin + SFX	None	MRND for advanced neck disease and for primary salvage
University of Chicago, phase II [49]	C/P weekly × 6	Paclitaxel, 5-FU, hydroxyurea + HF-XRT	None	MRND for advanced neck disease and for primary salvage
University of Pennsylvania, phase II [50]	C/P every 3 weeks × 2	Paclitaxel weekly + SFX	C/P every 3 weeks × 2	MRND for advanced neck disease and for primary salvage
MPCRN, phase II [51]	C/P every 3 weeks; continuous infusion 5-FU days 1-42	C/P weekly + SFX	None	MRND for advanced neck disease and for primary salvage
ECOG 2399, phase II	C/P every 3 weeks × 2	Weekly paclitaxel + SFX	None	MRND for advanced neck disease and for primary salvage
University of Michigan, phase II [52]	PF × 1	Cisplatin every 3 weeks + SFX	Paclitaxel every 3 weeks × 2	MRND for advanced neck disease and for primary salvage

Abbreviations: C/P = carboplatin/paclitaxel; HF-XRT = hyperfractionation radiotherapy; MPCRN = Minnie Pearl Cancer Research Network; MRND = modified radical neck dissection; PF = cisplatin + 5-fluorouracil (5-FU); SFX = standard fractionation radiotherapy; TAX = taxotere; TPF = docetaxel + cisplatin + 5-FU.

We suggest that multiple lines of evidence support the notion that sequential treatment represents an improvement over treatment with either induction chemotherapy or chemoradiotherapy and may represent the future of treatment for locally advanced SCCHN. Sequential treatment with an aggressive induction chemotherapy regimen leads to high response rates and enhanced complete response rates prior to chemoradiotherapy, reduced tumor volume, better functional outcome, and good systemic treatment, and is a prognostic test for more aggressive therapy. Rapid movement to chemoradiotherapy will increase local-regional dose intensity, which can be adjusted for response and prognosis after induction therapy and will minimize repopulation and expansion of partially resistant tumor cells while permitting functional primary site preservation. Finally, surgery can be used to remove areas of prior bulk or current residual disease, principally in the neck, and to salvage early recurrences. Phase III trials will soon be initiated to compare sequential treatment regimens with chemoradiotherapy in locally advanced SCCHN. These will determine the value of this concept; however, we predict that this form of treatment will accomplish a major change in prognosis for good performance status patients with locally advanced SCCHN.

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