Docetaxel in the treatment of squamous cell carcinoma of the head and neck

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Abstract: Squamous cell carcinoma of the head and neck (SCCHN) presents at a locally advanced (LA) stage in many patients. Chemotherapy has been successfully integrated into first-line treatment programs, either during or prior to radiotherapy (RT) – the cornerstone modality for local disease control of inoperable disease or when organ preservation is desired. Concomitant chemoradiotherapy (CCRT) provides an absolute survival benefit when compared with other types of locoregional therapy that exclude chemotherapy. Nonetheless, distant metastases still represent the most common cause of treatment failure. Consequently, adding induction chemotherapy (ICT) to definitive non-surgical local therapies with a curative intent has been vigorously explored in LA SCCHN. Recently, it has been shown that ICT using the combination of the taxane docetaxel with cisplatin–5-fluorouracil provides significant survival benefit over cisplatin–5-FU, when used before either definitive RT (TAX323 trial) or carboplatin-based CCRT (TAX324 trial). Docetaxel is also being investigated in metastatic or recurrent (M/R) disease, with promising initial results. It is very likely that the future management strategies of SCCHN will incorporate biologic agents as an add-on to docetaxel-containing schemas, administered either as ICT prior to CCRT in the LA setting or for the management of M/R disease.

Keywords: chemoradiotherapy, chemotherapy, docetaxel, head and neck carcinoma, induction, locally advanced, taxane

Introduction

With a global annual incidence of approximately 500,000 cases, squamous cell carcinoma of the head and neck (SCCHN) – which includes carcinomas of the oral cavity, floor of mouth, tongue, tonsils and juxtatonsillar fossae, larynx, and pharynx (oropharynx, epipharynx, and hypopharynx) – is the fifth most common cancer worldwide (Parkin et al 2005). Even in the US, where the incidence of SCCHN is relatively low, this type of cancer accounts for up to 3% of all malignant neoplasms (National Cancer Institute 2008a). SCCHN, an aggressive epithelial malignancy, has historically been associated with poor prognosis. Moreover, as the majority of SCCHN cases are associated with tobacco consumption and alcohol abuse, many patients present with notable comorbidities linked to lifestyle, a factor that limits the delivery of effective antitumor therapy. Indeed, up until the mid-1990s, 5-year survival rates had been reported to be as low as 30% or below for stage IVa/b (M0) disease (Vokes et al 1993), and 40% for stage III disease (Laramore et al 1992). However, over the last decade, overall mortality rates for cancers of the oral cavity, pharynx, and larynx have been modestly decreasing in the general population (National Cancer Institute 2008b, c). This is the case not only in low stage cancers, an effect mostly attributable to progressively earlier detection of curable tumors over time, but also in locally advanced (LA) disease. The latter effect is due to an interplay of numerous factors, including the continuous advances in oncologic supportive care, refinement of the manner of administration of complex chemotherapy regimens, technical advances in the delivery

of radiotherapy, optimization of surgical techniques (applied either in the primary or salvage setting), and last, but not least, an increased acceptance of the value of a multidisciplinary approach in the management of this disease. At this point, we believe that "state-of-the-art" delivery of aggressive therapy could potentially lead to 5-year survival rates in the range of 35% to 37% for stage IVa/b (M0) disease, and 44% to 46% for stage III disease. The above notwithstanding, the great effort behind these modest increases in survival continues to largely reflect the adverse biological determinants of this malignancy. These factors result in an overall aggressive clinical phenotype, ie, the frequent presence of locoregionally advanced disease at the time of initial presentation, as well as unfavorable patterns – or timing – of treatment failure in patients who eventually develop metastatic or recurrent (M/R) disease or second primary carcinomas of the upper aerodigestive tract and lung (Seiwert and Cohen 2005). Finally, it has been noted that even nowadays, and despite optimal delivery of curative-intent therapy for LA SCCHN, traditional approaches aiming at both excellent locoregional control and ultimate disease eradication can often be debilitating and occasionally disfiguring, and can lead to long-term devastating consequences for quality of life (eg, life-long enteral tube use for alimentation). Therefore, fostering further improvements in the methods of delivery of a complex multimodal treatment "package" is extremely important, especially if such an improvement could result in a significant decrease in the intensity of application of locoregional therapy, which remains the major cause for most of the irreversible and incapacitating side effects of currently applied treatment plans.

In the current Union Internationale Contre le Cancer/ American Joint Committee on Cancer (UICC/AJCC) staging system, stages III, IVa, and IVb comprise "LA SCCHN (M0)", and in contrast to other epithelial malignancies, only stage IVc is associated with distant metastatic (M1) disease (Greene et al 2002; Irish and Lee 2005). Patient outcomes have improved over the past 3 decades as a result of several advances, which include (among others): a) stepwise improvements in the concept of multimodality therapy (consisting of increasingly sophisticated combinations of surgery, radiotherapy [RT], and chemotherapy); b) application of technically expert single-modality therapy (when the latter is appropriately chosen in selected patients [eg hyperfractionated RT in stage III oropharyngeal carcinoma]); c) individual technical innovations within each discipline (eg the advent of intensity modulated or image-guided radiation therapy); and d) intensification of ancillary care methods (such as speech

therapy or nutritional support) (Miller 1990; Nelson 1998; Vokes 2005). However, successful treatment with curative intent of both LA and M/R SCCHN remains a formidable clinical challenge, and new treatment options and approaches are urgently needed. This is especially true for patients who are either not eligible for surgery, have low surgical curability rates, or harbor tumors for which non-surgical therapy represents a more acceptable – and arguably better – treatment (eg, RT or chemoradiotherapy for infiltrative LA tonsillar carcinomas). For all the above SCCHN patients, the combination of RT and cytotoxic chemotherapy, and more recently biologically targeted agents, has been the focus of intense clinical investigation, resulting in the launch of several important clinical trials.

To this end, this review presents an in-depth summary of novel data in the context of both treatment of LA disease (first-line) and management of recurrent (second-line) or metastatic disease (mainly first-line). Focus is given to the incorporation of the taxane, docetaxel, in the chemotherapy component of clinical treatment programs in an effort to maximize patient benefit.

Chemotherapy regimens used for the treatment of locally advanced SCCHN
Generalities

The integration of cytotoxic chemotherapy in the treatment of SCCHN has been the subject of clinical investigation for more than 3 decades. For example, when surgery is the chosen primary curative-intent therapy in patients with "resectable" LA SCCHN, single-agent or combination chemotherapy has been applied in both the preoperative (neoadjuvant or induction) and postoperative (adjuvant) settings. In the latter context, chemotherapy is generally used in combination with definitive postoperative RT (PORT), ie, postoperative chemoradiotherapy. Similarly, significant progress has been witnessed toward the integration of chemotherapy in clinical treatment programs for LA SCCHN in patients who are not surgical candidates, and in whom RT – as the cornerstone modality for local control – plays a major role toward achieving complete disease eradication. In the latter realm, cytotoxic chemotherapy can be administered during RT (ie, concomitant chemoradiotherapy [CCRT]) or can be used prior to RT (ie induction chemotherapy [ICT]). A novel treatment paradigm in LA disease is sequential therapy, in which ICT is followed by CCRT, in a sequence that may also include surgery for either exstirpation of residual/recurrent disease at the primary

site and/or regional nodal territories (surgical salvage) or, in the context of preplanned neck dissection, confirmation of pathologic complete response (pCR) in patients with bulky regional lymphadenopathy (stage $\geq$T $\times$ N2) at presentation. In the subsequent sections of this review, we will focus on the impact of chemotherapy in SCCHN patients who are not surgical candidates or who desire organ preservation (when the latter is realistically possible).

Several studies have shown that the exact manner of integrating a chemotherapy regimen with definitive RT has a significant bearing on overall survival (OS) of patients with LA SCCHN. In general, CCRT has been associated with a greater survival benefit than ICT treatment regimens, and the magnitude of this benefit has been dependent on the specific drug – or drug combination – used (Pignon et al 2000). This difference in treatment benefit in LA disease was shown by a large meta-analysis, which used updated individual patient data published by the investigators of the French Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) group. Locoregional treatment (RT and/or surgery) and locoregional treatment plus chemotherapy (delivered as either ICT or concomitantly with RT) were compared in terms of OS (Pignon et al 2000). The timing of chemotherapy was found to have a major effect on 5-year absolute survival benefit. Overall, ICT regimens were associated with no significant benefit compared with control regimens (locoregional definitive therapy upfront), although when the combination of cisplatin and 5-fluorouracil (PF) was given for ICT, there was a 5% absolute survival benefit. In this meta-analysis, CCRT resulted in a significant absolute survival rate benefit of 8% at 5 years (Pignon et al 2000). It should be noted at this point that ICT is not firmly established as part of the management plan specifically for LA squamous cell carcinoma of the oral cavity; radical surgical exstirpation of the primary tumor (typically followed by either PORT or postoperative CCRT) remains the therapy of choice in operable patients, and upfront CCRT is still widely employed in inoperable cases. The Pignon meta-analysis results represent a significant part of the scientific basis for the broad adoption of CCRT (especially RT combined with high-dose 3-weekly cisplatin) in clinical practice for the treatment of LA SCCHN in North America. In the specific context of maintenance of an anatomically intact larynx, CCRT has also been strongly advocated as the most successful strategy for non-operative larynx preservation, according to the published results of the Radiation Therapy Oncology Group 91–11 trial in which larynx preservation – rather than laryngectomy-free survival – was the primary endpoint (Forastiere et al 2003).

In the next section, the role of ICT followed by definitive locoregional, non-surgical therapy in the management of LA SCCHN will be discussed and juxtaposed to the CCRT treatment paradigm; once again, we will focus on the impact of incorporating docetaxel in the ICT portion of clinical treatment programs.

Docetaxel use in locally advanced disease

Over time, and along with the improved survival and locoregional control (LRC) achievable with the aforementioned schedules of CCRT delivery, a shift in the patterns of treatment failure has been observed. Historically, LRC represented the most important concern in LA SCCHN management, in that the occurrence of distant metastases (DMs) was relatively less common. However, increasingly sophisticated delivery of CCRT has led to LRC rates in excess of 90% and the emergence of DMs as the most frequent cause of treatment failure (Vokes et al 2000; Adelstein et al 2002). This observation suggested a possible role for adding further elements of systemic chemotherapy to the entire treatment "package" with the aim of improving global treatment success measures by decreasing the incidence of distal recurrence (Adelstein and Leblanc 2006). In view of the above issues, significant interest in adding ICT to definitive non-surgical local therapies has recently resurged.

Assuming ICT is selected for the upfront treatment of LA SCCHN (to be followed by local definitive therapy), a long-honored standard approach has been to deliver cisplatin and 5-fluorouracil (5-FU) (the PF doublet). The PF regimen was initially championed by Al-Sarraf et al (1998) as a highly active regimen against advanced nasopharyngeal carcinoma (NPC) when used as "consolidation" after CCRT, ie, in an adjuvant rather than an induction/neoadjuvant approach, as was the case in the seminal Intergroup (INT)-0099 trial. The use of the PF regimen was further refined during the next 2 decades, leading to its widespread use for the management of not only NPC, but progressively of LA SCCHN. PF ICT was especially favored in Latin Europe (France, Italy, and Spain), but was also used in parts of South America and East Asia, where it was accepted as a standard ICT regimen by many oncologists, who would consider its use in many patients, while other patients would receive upfront cisplatin-containing CCRT (Lefebvre and Bonneterre 1996; Seiwert and Cohen 2005).

In ICT early clinical trials, despite overall response rates (ORRs) and complete response (CR) rates as high as 90% and 50%, respectively, no consistent improvement in LRC or survival was demonstrated (Adelstein and Leblanc 2006).

It is of note, however, that in several of these ICT trials, DMs were indeed reduced among patients who received chemotherapy (Schuller et al 1988; Department of Veterans Affairs Laryngeal Cancer Study Group 1991; Paccagnella et al 1994). The lack of impact of this ICT-related reduction in DMs on OS was subsequently attributed to the historically limited importance of distant vs locoregional failure and the accompanying disease recognition and reporting bias. More recently, the taxanes – paclitaxel, but also docetaxel – have shown promising initial activity in various preliminary clinical studies in SCCHN patients, in both locally advanced and disseminated/recurrent settings. Consequently, over the last few years, several investigators have addressed the effect of adding taxanes to PF-based ICT in order to increase the efficacy of the PF doublet and improve OS in patients with LA SCCHN (Hitt et al 2002, 2005; Posner and Lefebvre 2003; Fountzilas et al 2005a; Rapidis et al 2006; Posner et al 2007; Vermorken et al 2007).

In a randomized phase III study of 382 patients with LA head and neck cancer, ICT comprising paclitaxel in addition to cisplatin and 5-FU (Pacli-PF) – followed by cisplatin CCRT – achieved a higher response rate (RR), increased time to treatment failure, and was better tolerated than ICT with PF alone (Hitt et al 2005). Patients received either PF (cisplatin 100 mg/m^2 Day 1 plus 5-FU 1000 mg/m^2 continuous infusion on Days 1–5) or Pacli-PF (paclitaxel 175 mg/m^2 Day 1, cisplatin 100 mg/m^2 Day 2 and 5-FU 500 mg/m^2 continuous infusion on Days 2–6) for 3 cycles every 21 days. Additional CCRT with cisplatin (100 mg/m^2 Days 1, 22, and 43) and RT (70 Gy) was administered to patients with a CR or partial response (PR), $\geq 80\%$ in the primary tumor site. A CR was observed in 33% of patients in the Pacli-PF arm vs 14% in the PF arm (p $<$ 0.001); median time to treatment failure (TTF) was 20 months vs 12 months (log-rank p = 0.006) in the Pacli-PF and PF arms, respectively, and median OS was 43 months vs 37 months, respectively (log-rank p $<$ 0.06). The overall incidence of acute grade 3/4 adverse events (AEs) (Pacli-PF vs PF, respectively) was similar in the two treatment arms (60% vs 68%); however, compared with Pacli-PF, PF was associated with significantly more grade 2–4 mucositis (16% vs 53%) during ICT, grade 3/4 mucositis (34% vs 55%) during CCRT, and grade 3/4 nausea and vomiting (4% vs 17%). Grade 3/4 neutropenia was more common with Pacli-PF than PF (32% vs 20%).

Although the above study by Hitt and colleagues demonstrated the feasibility of delivering the Pacli-PF ICT combination prior to cisplatin-CCRT, the relative dearth of antecedent experience with paclitaxel-based induction regimens in the management of LA head and neck cancer is noteworthy, and deserves further comment here. Indeed, although early clinical (mainly phase I) data with Pacli-cisplatin ICT in LA SCCHN were reported as early as 1995 (Hitt et al 1995), the momentum in advancing the clinical development of paclitaxel-based regimens for ICT was not maintained, as evident by the 10-year period separating the aforementioned studies by Hitt's group. Nevertheless, some interest in this regimen continues (Barone et al 2008). Similarly, the Pacli-PF triplet was not clinically studied to a significant extent in a large cooperative group setting (either in the US or the EU) until the reporting in 2006 of efficacy data in the metastatic (advanced) or recurrent – rather than LA – setting by the Head and Neck Working Group of the US Southwest Oncology Group (SWOG) (S0007 study) (Worden et al 2006). Moreover, the concept of paclitaxel-based ICT has not been advanced in NPC since the mid 1990s. Indeed, it was only in 2005 that preliminary efficacy data were reported on the combination of cisplatin, epirubicin, and paclitaxel (CEP) ICT followed by Pacli-CCRT in LA NPC, in a phase I/II study by the Hellenic Cooperative Oncology Group (HeCOG) (Fountzilas et al 2005b). The above situation with paclitaxel is in stark contrast with the wealth of data emanating from the clinical development of docetaxel in both SCCHN and NPC since the mid 1990s. Indeed, the integration of docetaxel in ICT schemas for both malignancies was promulgated by numerous clinical investigator groups, resulting in early reporting of impactful phase II data on both efficacy and deliverability of such schemas. One of these phase II studies focused on docetaxel (Taxotere®)–cisplatin–5-fluorouracil (TPF) ICT in LA SCCHN; in this study, Posner et al (2001) reported a post-ICT overall response rate (complete response + partial response [CR + PR] of 93%, along with a pathologically confirmed CR (pCR) of 92% in patients with clinical CR and 54% in those with clinical PR. A second, conceptually similar phase II study in LA NPC patients by Glisson's group demonstrated that docetaxel-carboplatin (TCb) ICT followed by RT – or CCRT in a minority of cases – resulted in a post-ICT overall response rate of 89%, accompanied by estimated 3-year progression-free survival (PFS) and OS rates of 54% and 74%, respectively (Johnson et al 2004). In view of the above, it becomes evident that docetaxel-containing regimens yielded more robust and abundant clinical data regarding the management of head and neck carcinoma than chemotherapy combinations containing paclitaxel.

One further comment is in order here regarding the different properties of the two clinically active taxanes in

SCCHN, namely paclitaxel and docetaxel. Although both agents share a common mechanism of action involving tubulin polymer stabilization and cell-cycle arrest, docetaxel demonstrates a higher affinity for β-tubulin, a longer intracellular half-life, as well as the ability to promote stabilization of microtubules at significantly lower molar concentrations than paclitaxel (Schrijvers and Vermorken 2005). Although, in principle, both paclitaxel and docetaxel may be combined with PF to improve ICT efficacy (Kies et al 2006), the potential for overlapping neuropathy with paclitaxel and cisplatin – especially when both agents are used at the higher end of their dosage range – has been recognized as potentially significant. Further, the generally more predictable (and hence manageable) toxicity profile of docetaxel compared with paclitaxel (when the latter is used at a higher dose range) has led to an increased interest in docetaxel-based therapy (Hitt et al 2006b).

The docetaxel–cisplatin–5-fluorouracil (TPF) regimen

TPF as ICT prior to local/regional definitive therapy

Over the last decade, several phase I and II studies have investigated the combination of docetaxel with PF-based induction therapy (the TPF regimen) in patients with LA SCCHN (Table 1). Study results for this combination were encouraging, with high overall response rates (ORRs) (71%–100%) and promising long-term survival (62%–78% at 3 years) (Colevas et al 1998, 1999, 2002; Janinis et al 2001; Posner et al 2001; Watanabe et al 2003; Schrijvers et al 2004; Tsukuda et al 2004). Following these results, a seminal phase III study was undertaken to assess the efficacy and safety of TPF given as ICT prior to RT – the European Organisation for Research and Treatment of Cancer (EORTC) 24971/TAX 323 trial.

TPF followed by definitive RT: TAX 323

TAX 323 was a phase III trial that investigated TPF induction therapy followed by RT in patients with LA, unresectable SCCHN (Remenar et al 2006; Vermorken et al 2007). A total of 358 patients were enrolled, stratified by primary disease site, and randomized to receive either TPF (docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 Day 1, plus 5-FU 750 mg/m^2 Days 1–5, every 3 weeks for 4 cycles) or PF (cisplatin 100 mg/m^2 Day 1 plus 5-FU 1000 mg/m^2 Days 1–5, every 3 weeks for 4 cycles). Following ICT, patients received conventional, accelerated, or hyperfractionated RT according to investigator or institutional choice,

with surgery permitted either prior to RT, or at 3 months after completion of RT (depending on specific response thresholds). The study primary endpoint was PFS, with secondary endpoints of OS, tumor response, safety, and quality of life (QoL).

Compared with PF, ICT with TPF was associated with significantly longer median PFS and OS (hazard ratios [HR] 0.72 [95% confidence interval {CI}: 0.56–0.93; p = 0.028] and 0.70 [95% CI: 0.55–0.89; p = 0.0042], respectively), while ORRs and CR rates (pre- and post-RT) were also significantly higher in the TPF group (Table 2). The tolerability profile of the TPF regimen was deemed to be favorable. While the incidence of febrile neutropenia was higher with TPF, it was predictable based on the tolerability profile of docetaxel and did not increase the incidence of treatment-related deaths (Table 2). The incidences of stomatitis/mucositis and thrombocytopenia were higher in the PF treatment arm than in the TPF arm, while the incidences of leukopenia, neutropenia, and alopecia were lower. Dose reductions due to toxicity were more common in the PF treatment arm compared with the TPF arm (10.0% vs 3.5%, respectively). In addition, the PF arm was associated with a higher incidence of dose delays (38.0% vs 2.0%, respectively), treatment discontinuations due to AEs (12.0% vs 6.0%, respectively), and deaths due to treatment-related toxicity (7.8% vs 3.7%, respectively). It is notable that with regard to mucosal local toxicity observed in TAX 323, the triplet TPF regimen was, overall, more tolerable than the PF regimen because of the significantly reduced cumulative dose of 5-FU in the TPF vs PF ICT regimen (15 g/m^2 vs 20 g/m^2, respectively).

In addition to standard efficacy endpoints, TAX 323 compared the effect of TPF and PF on QoL indices. QoL was assessed using the EORTC QoL Global Health Questionnaire C30 (QLQ-C30) and the Performance Status Scale for Head and Neck patients (PSS-HN) standardized form. Patients receiving TPF had significantly improved QLQ-C30 scores compared with those receiving PF (p = 0.01) and had a longer time to first deterioration in World Health Organization (WHO) performance status (PS) (p = 0.0158). On the PSS-HN measure, TPF ICT was associated with significant improvement in score for 3 key components of the scale – intake of normal diet (p = 0.0064), understandability of speech (p < 0.0001), and ability to eat in public (p = 0.002).

TPF followed by CCRT: TAX 324

TAX 323 provided the basis for the use of docetaxel in the context of TPF ICT in combination with definitive

Table 1 Docetaxel–cisplatin–5-fluorouracil in phase I/II studies in squamous cell carcinoma of the head and neck

Reference	Regimen	Patients, n	Complete RR, %	ORR, %	OS, %		
					1-year	2-year	3-year
Colevas et al (1998)	Docetaxel 25–60 mg/m² D1	23	61	100	100	83	78
	Cisplatin 25 mg/m² D1-5						
	5-FU 700–800 mg/m² D1-5						
	Leucovorin 500 mg/m² D1-5						
Colevas et al (1999)	Docetaxel 60 mg/m² D1	30	63	93	83	80	77
	Cisplatin 31.25 mg/m² D1-4						
	5-FU 700–800 mg/m² D1-4						
	Leucovorin 500 mg/m² D1-4						
Colevas et al (2002)	Docetaxel 60–95 mg/m² D1	34	44	94	82	68	62
	Cisplatin 100 mg/m² D1						
	5-FU 700 mg/m² D1-4						
	Leucovorin 500 mg/m² D1-4						
Posner et al (2001)	Docetaxel 75 mg/m² D1	43	40	93	98	79	77
	Cisplatin 100 mg/m² D1						
	5-FU 1000 mg/m² D1-4						
Janinis et al (2001)	Docetaxel 80 mg/m² D1	20	20	90	85	60	–
	Cisplatin 40 mg/m² D2-3						
	5-FU 1000 mg/m² D1-3						
Schrijvers et al (2004)	Docetaxel 75 mg/m² D1	48	0	71	69	41	–
	Cisplatin 75–100 mg/m² D1						
	5-FU 750 mg/m² D1-5						
Tsukuda et al (2004)	Docetaxel 60–70 mg/m² D1	18	22	94	–	–	–
	Cisplatin 60–70 mg/m² D4						
	5-FU 600–750 mg/m² D1-5						
Watanabe et al (2003)	Docetaxel 48 mg/m² D1	34	59	88	–	93	–
	Cisplatin 24 mg/m² D1-4						
	5-FU 560 mg/m² D1-5						
	Leucovorin 500 mg/m² D1-4						

Abbreviations: 5-FU, 5-fluorouracil; ORR, overall response rate; OS, overall survival; RR, response rate.

RT. However, given the results of TAX 323, RT alone is no longer considered adequate treatment for LRC. As such, the efficacy and tolerability of TPF ICT compared with standard PF was further investigated in a second large phase III trial, TAX 324, in which ICT was followed by carboplatin (Cb)-based CCRT (Posner et al 2007). In this multicenter, randomized trial, 501 patients with LA, histologically confirmed SCCHN who had received no previous chemotherapy, radiation, or surgery received either TPF (docetaxel 75 mg/m² and cisplatin 100 mg/m² Day 1, plus 5-FU 1000 mg/m² Days 1–4, every 3 weeks for 3 cycles) or PF (cisplatin 100 mg/m² Day 1 plus 5-FU 1000 mg/m² Days 1–5, every 3 weeks for 3 cycles) followed by CCRT, which was planned to deliver daily radiation

Table 2 TAX 323: select efficacy and safety results

Results	PF	TPF
Efficacy	n =181	n = 177
Median PFS, months	8.2	11.0[a]
Median OS, months	14.5	18.8[b]
Response rates, %		
ORR, chemotherapy alone	54	68[c]
ORR, chemotherapy + radiation	59	72[d]
Complete RR, chemotherapy alone	6.6	8.5
Complete RR, chemotherapy + radiation	19.9	33.3[e]
Major safety	n = 179	n = 173
Grade 3/4 hematologic toxicity, % patients		
Leukopenia	22.9	41.6
Neutropenia	52.5	76.9
Thrombocytopenia	17.9	5.2
Anemia	12.8	9.2
Febrile neutropenia	2.8	5.2
Grade 3/4 non-hematologic toxicity, % patients		
Alopecia	0	11.6
Anorexia	3.4	0.6
Infection	6.1	6.9
Stomatitis	11.2	4.6

[a]p = 0.007 vs PF; [b]p = 0.002 vs PF; [c]p = 0.006 vs PF; [d]p = 0.0063 vs PF; [e]p = 0.004 vs PF.

Abbreviations: ORR, overall response rate; OS, overall survival; PF, cisplatin–5-fluorouracil; PFS, progression-free survival; RR, response rate; TPF, docetaxel + cisplatin + 5-fluorouracil.

for 5 days per week simultaneously with weekly Cb at an area under the curve (AUC) of 1.5 (Calvert formula). The primary endpoint was OS, with secondary endpoints including PFS and safety.

The results of TAX 324 demonstrated a 14% absolute improvement in 3-year survival, with a 30% reduction in risk of death for ICT with TPF compared with PF. Median OS was significantly longer in the TPF arm compared with the PF arm (71 months vs 30 months; HR: 0.70; 95% CI: 0.54–0.90; p = 0.006), with survival rates at 1, 2, and 3 years and pre- and post-CCRT response rates (RRs) also higher in the TPF arm (Table 3).

As with TAX 323, the overall incidence of grade 3/4 hematologic toxicities was predictably higher in the TPF arm than in the PF arm, including neutropenia (83% vs 56%, respectively), febrile neutropenia (12% vs 7%, respectively), and neutropenic infection (12% vs 8%, respectively). In parallel to the differential AE profiles seen between the 2 arms of TAX 323, PF was associated with a higher incidence of grade 3/4 stomatitis, lethargy, vomiting, and altered hearing compared with TPF in the TAX 324 trial (Table 3).

Other trials of TPF induction + CCRT VS CCRT alone

Two phase II/early phase III trials are currently underway, both of which have recently provided preliminary data suggesting that ICT with TPF followed by CCRT may be more effective than CCRT alone in unresectable LA SCCHN. In the first study, patients in Arm A received 2 cycles of cisplatin 20 mg/m^2 Days 1–4 plus 5-FU 800 mg/m^2 over a 96-hour continuous infusion at weeks 1 and 4 of RT (66–70 Gy); patients in Arm B received ICT with TPF (docetaxel 75 mg/m^2 and cisplatin 80 mg/m^2 Day 1, plus 5-FU 800 mg/m^2 over a 96-hour continuous infusion), followed by the same CCRT regimen as in Arm A (Ghi et al 2006). Preliminary efficacy results showed a radiologic CR in 64% (95% CI: 45%–80%) of patients in Arm B, compared with 20% (95% CI: 8%–37%) in Arm A. During CCRT, grade 3/4 AEs occurring in Arms A and B, respectively, were mucositis (42% vs 26%, respectively), dysphagia (20% vs 9%), skin reaction (12% vs 8.6%), asthenia (5% vs 3%), grade 3 weight loss (2% vs 3%), and grade 3 mouth dryness (0% vs 3%). Grade 3/4 granulocytopenia occurred in 56% of patients receiving TPF ICT, while febrile neutropenia occurred in 7.5% of patients in this group.

Table 3 TAX 324: select efficacy and safety results

Results	PF	TPF
Efficacy	n = 246	n = 255
OS		
Median, months	30	71[a]
2-year, %	55	67
3-year, %	48	62
PFS		
Median, months	13	36[b]
2-year, %	42	53
3-year, %	37	49
Response rate, %		
ORR, post-chemotherapy	64	72[c]
CR, post-chemotherapy	15	17[d]
Major safety	n = 243	n = 251
Grade 3/4 hematologic toxicity, % patients		
Neutropenia	56	83
Febrile neutropenia	7	12
Neutropenic infection	8	12
Grade 3/4 non-hematologic toxicity, % patients		
Stomatitis	27	21
Lethargy	10	5
Vomiting	10	8
Diarrhea	3	7
Nausea	14	14

[a]p = 0.006 vs PF; [b]p = 0.004 vs PF; [c]p = 0.07 vs PF; [d]p = 0.66 vs PF.
Abbreviations: CR, complete response; ORR, overall response rate; OS, overall survival; PF, cisplatin–5-fluorouracil; PFS, progression-free survival; TPF, docetaxel + cisplatin + 5-fluorouracil.

In the second study, 295 patients received 3 cycles of ICT with either TPF (docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 Day 1, plus 5-FU 750 mg/m^2 Days 1–5, every 3 weeks, plus granulocyte-colony stimulating factor and antibiotic prophylaxis with ciprofloxacin) or PF (cisplatin 100 mg/m^2 Day 1, followed by 5-FU 1000 mg/m^2 Days 1–5, every 3 weeks) (Hitt et al 2006b). Each induction regimen was followed by CCRT, delivered as conventional RT (up to 70 Gy) plus concomitant cisplatin 100 mg/m^2 on Days 1, 22, and 43. Patients in a third treatment arm received conventional CCRT alone. In this study, ICT followed by CCRT resulted in a higher CR rate compared with CCRT alone (70% vs 49%, respectively; p = 0.02), although there was no difference between the PF and TPF induction groups. Time to progression (TTP) was longest in the TPF group (16 months), followed by PF (12 months) and CCRT alone (8 months) (log-rank p = 0.02). Mucositis occurred in 60% of patients in the PF group, 55% in the TPF group, and 36% in the CCRT alone group. Final results, including OS and PFS data, are eagerly awaited for both aforementioned trials.

TPF induction therapy plus RT for organ preservation: GORTEC 2000–01

TPF induction followed by RT may also be beneficial in terms of organ preservation, which can be an important factor to consider in the treatment of head and neck cancer. The French Groupe d'Oncologie Radiotherapie Tete et Cou (GORTEC) 2000–01 study randomized 220 patients with cancer of the hypopharynx or larynx to ICT with TPF or PF, followed by RT (Calais et al 2006). TPF followed by RT provided larynx preservation in 80% of patients, compared with 57.6% of patients receiving upfront PF. Compliance was also greater in the TPF arm, which was associated with a higher ORR (82.8% vs 60.8%; p = 0.0013) and improved tolerability of the entire treatment sequence.

Docetaxel-containing doublets/triplets administered as concurrent chemoradiotherapy: TP ± F CCRT trials

As mentioned in previous sections, the aim of CCRT is to deliver systemically active chemotherapeutic agents, while

capitalizing on their radiosensitizing activity; this treatment approach is associated with promising efficacy, and has become the dominant treatment modality for certain SCCHN subtypes (such as nasopharyngeal carcinoma) in many tertiary centers (Hoffman et al 2004). Several recent studies have shown that docetaxel-cisplatin (TP) CCRT combination therapies are reasonably well tolerated and moderately effective, with high ORRs (Bouillet et al 2007; Kandil et al 2007; Minea et al 2007; Sayed et al 2007; Tsao et al 2007).

These early phase trials are encouraging with regard to the efficacy of the docetaxel–cisplatin combination when it is delivered concomitantly with RT. However, docetaxel is not approved for CCRT or for palliative use, and phase III studies are needed in order to support these data and further evaluate late side effects.

Concurrent TPF CCRT vs TPF induction followed by radiation therapy

In a trial of 30 patients with LA SCCHN, TPF CCRT was more effective than TPF ICT followed by RT, although it was associated with more toxicity and required more supportive care (Katori et al 2005). Patients in the induction therapy group received 2 cycles of docetaxel 60 mg/m^2 Day 1, cisplatin 70 mg/m^2 Day 4, and 5-FU 750 mg/m^2/day Days 1–5, followed by RT (as the sole modality for definitive local/regional treatment), starting 21 days after completion of chemotherapy, while patients in the TPF CCRT group received 2 cycles of docetaxel 50 mg/m^2 Day 1, cisplatin 60 mg/m^2 Day 4, and 5-FU 600 mg/m^2/day Days 1–5, concomitantly with radiation (1.8–2.0 Gy/fraction/day) starting on the first day of chemotherapy. The total radiation dose delivered was 64 to 70 (mean 66.9) Gy in the TPF induction group and 63.0 to 74.0 (mean 67.8) Gy in the TPF CCRT group. While the ORR and CR rates were similar in both groups (ORR: 100% in both groups; CR: 84% for the induction TPF group vs 87% for the TPF CCRT group), the 3-year survival rate was significantly higher with concurrent TPF chemoradiotherapy compared with induction TPF chemotherapy followed by RT alone (83% vs 64%, respectively; p = 0.029). However, the AE rate was higher in the TPF CCRT treatment group. Not unexpectedly, mucositis and anemia were significantly more prevalent with concurrent TPF compared with induction TPF (79% vs 40%, and 16% vs 0%, respectively), as one of the consequences of exploiting the radiosensitizing properties of chemotherapy within a CCRT regimen is that adjacent normal tissue within the field is also subject to more effective – and more toxic – RT.

TPF CCRT: hyperfractionation vs conventional fractionation of the RT component

Hyperfractionation of RT within a given CCRT regimen may further improve RRs compared with conventional fractionation. In a study of 44 patients with previously untreated stage III-IV SCCHN, local-regional disease control, disease-free survival (DFS), and OS improved with TPF given concurrently via hyperfractionated RT compared with TPF given concurrently with conventionally fractionated RT (Katori et al 2006). All patients received docetaxel 50 mg/m^2 Day 1, cisplatin 60 mg/m^2 Day 4 plus 5-FU 600 mg/m^2 Days 1–5, every 4 weeks for 2 cycles, plus either hyperfractionated CCRT (1.2 Gy/fraction, twice daily 5 days per week to a total of 76.8 Gy/64 fractions) or conventionally fractionated CCRT (2 Gy/fraction/day, 5 days per week to a total of 70 Gy/35 fractions).

In the CCRT arm using hyperfractionated radiation delivery (hyperfractionated CCRT), the overall clinical response and pCR rates were 100% and 90%, respectively, compared with 100% and 81% in the conventional fractionation arm. However, and perhaps unsurprisingly, the incidence of mucositis was higher with hyperfractionation (p = 0.048). Trends to improvement with TPF given concomitantly with hyperfractionated CCRT were observed at 2 years for LRC vs conventional fractionation (90% vs 74%; p = 0.085), DFS (80% vs 64%; p = 0.091), and OS (90% vs 72%; p = 0.080).

Although the studies reported by Katori and colleagues (Katori et al 2005, 2006) are small and the conclusions on treatment benefit should be made with caution, the results are not isolated and provide further supporting evidence that TPF hyperfractionated CCRT is more effective than either TPF ICT followed by RT or TPF CCRT using conventional RT fractionation.

Role of TPF in management of LA disease

Results from several studies presented above, and most decidedly the pivotal TAX 323 and TAX 324 clinical trials, demonstrate that the addition of docetaxel to the PF regimen results in significantly improved efficacy, establishing TPF as a highly effective ICT combination regimen for the treatment of LA SCCHN. Of note, in the MACH-NC meta-analysis (Pignon et al 2000), while the addition of ICT in general (any combination regimen) did not offer a statistically significant benefit in terms of OS, a post hoc analysis of the ICT trials using specifically the PF combination showed a significant absolute benefit of 4% in 5-year survival. Taking into consideration the limitations of subgroup post hoc secondary analyses within a large meta-analysis, we consider this

difference due to PF ICT to be significant. Nevertheless, if one integrates this information with the benefits gained from the addition of docetaxel to PF ICT, it is logical to assume that the OS benefit from TPF ICT followed by RT alone would be >4% in 5 years. This benefit would then approach the absolute survival benefit associated with platinum-based CCRT. Similar arguments have been put forward by Pignon and collaborators in their report of an analysis of all the TPF phase I and II studies that preceded the pivotal TAX 323 and TAX 324 trials (Pignon et al 2004). Consequently, TPF represents an advance in the systemic aspect of multimodality treatment for LA SCCHN, and may provide an important paradigm shift in the treatment of this disease. While recognizing the proven value of platinum-based CCRT as a curative-intent management standard for LA SCCHN (especially in North America), we can surmise that TPF ICT has at least the potential to become another standard of care in this indication, with efficacy results possibly comparable to CCRT. Further, the TPF ICT regimen is well poised to provide an effective backbone for further refinement, including modification of the platinum and fluoropyrimidine components of ICT, as well as the platinum – and/or fluoropyrimidine – component of CCRT, and the addition of biologically targeted agents.

At this point, the tolerability profile of the TPF combination warrants mentioning. Based on the known side effect profiles for each of the drug components of this triplet, TPF represents a regimen with a generally predictable AE profile, which enables effective disease management. Nevertheless, strict enforcement of dose reductions, dose delays, and other regimen modifications as needed, and careful patient selection (especially regarding performance status) are required. Additionally, there is a need for careful monitoring for neutropenia (a major docetaxel side effect), which was observed (any grade) in 12.1% of patients receiving TPF in TAX 324 (Posner et al 2007). The prompt management of infections as well as their complications is also necessary, the rate of neutropenic infection in the TPF arm of TAX 324 being 11.7%. Moreover, in the TAX 324 TPF cohort, the incidence of grade 3 and 4 "venous system events," which include superficial and deep venous thrombosis, thrombophlebitis, and pulmonary embolism, was low (2.4%) (Posner et al 2007). Although venous thromboembolism is not part of the US Food and Drug Administration (FDA) "black box" warning statement with the docetaxel label (Taxotere label, Sanofi-Aventis), there are anecdotal observations of venous thrombosis occurrences (Feenstra et al 2000), which may be of considerable risk and inconvenience, particularly in SCCHN patients. Both thrombosis and infec-

tion, not only related to docetaxel use, are indeed relevant to patients with prolonged need for central intravenous access, which typifies many patients with LA SCCHN.

In view of the aforementioned efficacy and tolerability data, TPF has an important role in the re-establishment of ICT as an accepted approach in the management of selected LA SCCHN patients. Of note, TPF ICT followed by carboplatin-CCRT is also approved by both the US Federal Drug Administration (US FDA 2007) and the European Medicines Agency (EMEA) (EMEA 2007) for the treatment of LA SCCHN. Several pivotal trials are currently investigating this potential (Table 4), including DeCIDE and PARADIGM, two ongoing, international, multicenter, randomized, pivotal phase III studies comparing upfront TPF induction therapy followed by CCRT vs CCRT alone. Notably, the DeCIDE trial will evaluate the potential of TPF followed by an intensive CCRT regimen, in contrast to most studies that have to date used relatively "milder" CCRT. Moreover, the importance of gauging the effects of adding upfront TPF on organ preservation, a highly relevant endpoint in LA SCCHN, is reflected in another large study, the TREMPLIN trial, which is investigating larynx preservation in approximately 150 patients in France (Table 4). The role of ICT prior to surgery, especially in patients with large primary lesions, remains to be established and should be examined in phase II studies while awaiting results from the above large phase III trials. Such future phase II trials, as well as an analysis of the patterns of failure and use of surgery (either intercalated between ICT and RT or CCRT, or as salvage following the completion of the delivery of the entire treatment program) by secondary data mining from the TAX 323 and TAX 324 trials will also offer considerable insight to the degree and timing of TPF effects on local/regional disease control. This is much needed information, as delineating these effects could ultimately lead to modification of the CCRT component that would follow ICT, or even introduce the possibility of surgical definitive therapy post-ICT (the latter in highly selected patients). This is especially important in the era of targeted therapy agents and less extensive surgical approaches (eg, supracricoid subtotal laryngectomy and its variants), which will be predictably integrated in the sequential treatment program (ICT followed by CCRT ± surgery) in the near future.

Docetaxel in metastatic or recurrent disease

Despite optimal therapy, local or regional recurrence occurs in more than 50% of patients with SCCHN, with

approximately 30% of such patients developing distant metastases (Gedlicka et al 2002). Although initial presentation with metastatic (M1) disease is relatively rare (Hitt et al 2006a), chemotherapy in the context of recurrent or metastatic disease has, until recently, been largely palliative in nature. The promising activity of docetaxel given alone or in combination with other agents, however, has been investigated in several recent studies, and may provide the basis for improved outcomes in patients who currently face a very poor prognosis.

Docetaxel alone or in combinations for metastatic or recurrent SCCHN

Docetaxel monotherapy

Docetaxel monotherapy has been investigated in 3 recent trials. In the first, docetaxel (40 mg/m^2/week until disease progression or limiting toxicity) monotherapy was compared with methotrexate (40 mg/m^2/week until disease progression or limiting toxicity) monotherapy (Guardiola et al 2004), and was associated with a significantly higher objective RR (27.0% [95% CI: 21.7%–32.3%] vs 15.0% [95% CI: 11.2%–18.8%], respectively) in 57 patients with recurrent (n = 28) or metastatic (n = 29) SCCHN. The median response duration was longer with docetaxel (8.6 [range 1.7–17.6] months vs 6.2 [range 2.8–10.6] months), although the time to progression (TTP) and OS endpoints were similar between the 2 groups (1.97 [range 1–19] and 3.7 [range 0.13–10.0] months, respectively, for docetaxel monotherapy, vs 1.5 [range 1.0–12.0] and 3.9 [range 0.2–11.8] months, respectively, for methotrexate monotherapy). In this trial, side effects, particularly hematologic events, were more common in the docetaxel arm.

In a non-comparative phase II trial of weekly docetaxel monotherapy (30 mg/m^2 every 4 out of 5 weeks, to a maximum of 6 cycles), the ORR was 42% among 38 patients with M/R SCCHN (Hitt et al 2006a). The median response duration for patients with PR was 8.39 (95% CI: 8.28–11.5) months, with a median TTP of 10 months. Median OS was 11.3 months, with a 1-year survival rate of 39%. It is notable that no grade 3 or 4 AEs were reported.

The third monotherapy trial investigated weekly docetaxel 35 mg/m^2 for 3 out of every 4 weeks (Koussis et al 2007). A total of 24 patients with recurrent or metastatic SCCHN were enrolled in this study, all of whom had previously received platinum-based therapy. There were 6 PRs (25%) with a mean duration of 3.4 months. Stable disease (SD) was observed in 6 patients (25%) and progressive disease in 12 patients (50%). Toxicity was mild and consisted

of grade 4 mucositis in 3 patients (12.5%) and grade 3/4 hematologic toxicity in 4 patients (17%).

Docetaxel doublet chemotherapy

As the TPF triplet has shown significant activity in the LA disease setting, docetaxel has been investigated in the recurrent or metastatic disease setting as a doublet combination with one of the other two components of TPF. The most commonly investigated combination regimens are based on docetaxel plus cisplatin; this combination has achieved RRs of 42% to 80% and median OS durations of 10 to 13 months (Table 5) (Gedlicka et al 2002; Yabuuchi et al 2003; Hehr et al 2005; Baghi et al 2006; Guntinas-Lichius et al 2006; Peyrade et al 2006).

In a phase III study, 568 patients with locally recurrent or metastatic SCCHN received either docetaxel 75 mg/m^2 plus cisplatin 75 mg/m^2 on Day 1, every 3 weeks (TP), or cisplatin 100 mg/m^2 on Day 1 followed by 5-FU 1000 mg/m^2/day for 5 days, every 3 weeks (PF). For the primary endpoint of median TTP, the difference between groups was not statistically significant (p = 0.25); median TTP was 2.8 months in the TP group (95% CI: 2.6–3.7 months) vs 3.2 months in the PF group (95% CI: 2.9–3.9). The incidences of grade 3/4 leukopenia and grade 3/4 neutropenia were higher in the TC group (59.9% and 70.1%, respectively) than in the CF group (38.1% and 51.7%, respectively). Conversely, thrombocytopenia was more common in the CF group than in the TC group (all grades, 42.6% vs 16.6%; grade 3/4, 15.1% vs 4.8%, respectively) (ClinicalStudyResults.org 2008).

Docetaxel has also been investigated in combination with other cytotoxic agents. Docetaxel plus the vinca alkaloid vinorelbine was active in 29 heavily pretreated patients with recurrent SCCHN (Airoldi et al 2003). In this study, patients (21 with local-regional recurrence, 8 with metastatic disease) had been previously treated with CCRT (n = 14), surgery plus adjuvant RT (n = 13), surgery plus CCRT (n = 1), or RT alone (n = 1); 9 patients had received ≥1 courses of palliative chemotherapy. Docetaxel (80 mg/m^2) and vinorelbine (20 mg/m^2) were administered on Day 1 every 3 weeks for a maximum of 6 cycles.

The ORR was 49%, including 3 CRs (10%; median duration ≥20 months) and 11 PRs (38%; median duration 5.5 months). The most frequent serious AE was neutropenia (grade 3, 21%; grade 4, 79%). The first 12 patients experienced grade 3 (14%) and grade 4 (7%) infection, but with the addition of ciprofloxacin prophylaxis, the following 17 patients did not experience this type of event.

Table 4 Ongoing pivotal trials of docetaxel-based chemotherapy (Clinicaltrials.gov 2008)

Name	Sponsor/ collaborator	Primary investigator	Primary site	Planned patient no
Cooperative group or independent investigator-initiated clinical trials				
→ Pivotal trials				
1 A phase III trial of docetaxel-based chemoradio-therapy plus or minus induction chemotherapy to decrease events in head and neck cancer in N2/N3 stage patients (the DeCIDE trial) UofC IRB #: I3362B	University of Chicago	Ezra Cohen, Everett Vokes (co-PIs, University of Chicago, Chicago, IL, USA)	International multicenter	400
2 A phase III study of sequential therapy with TPF/ chemoradiation vs cisplatin-based chemoradio-therapy with accelerated concomitant boost RT for LA squamous cell cancer of the head and neck (the PARADIGM trial) DFCI trial #: 04–006	Dana-Farber Cancer Institute (DCFI)	Marshall Posner, Robert Haddad (co-PIs, DCFI, Boston, MA, USA)	International multicenter	330
→ Other trials (combining docetaxel with biologics)				
3 Larynx preservation with induction chemo-therapy (cisplatin, 5-FU, docetaxel) followed by RT combined with either cisplatin or cetuximab in laryngopharyngeal squamous cell carcinoma – a randomized phase II study (the "TREMPLIN" study)	Groupe Oncologie Radiother-apie Tete et Cou (GORTEC) Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC)	Jean-Louis Lefebvre (PI, Centre Oscar Lambret, Lille, France)	France, multicenter	156
4 Phase II trial of combination weekly bortezomib (Velcade®) and docetaxel (Taxotere®) in patients with recurrent and/or metastatic head and neck squamous cell carcinoma (VICC study #: HN0501)	Vanderbilt-Ingram Cancer Center (VICC) NCI	Christine Chung (Study Chair, VICC, Nashville, TN, USA)	US, multi-center	50
5 A phase II study of bevacizumab (Avastin®) in combination with docetaxel and radiation on LA squamous cell cancer of the head and neck (CASE CCC Study #: 6304)	Case-Western Reserve – Ireland Compre-hensive Cancer Center (CWRU ICC) NCI	Panos Savvides (Study Chair, Case Compre-hensive Cancer Center, Cleveland, OH, USA)	Case Comprehensive Cancer Center, Cleveland, OH, USA)	30
6 Phase III trial of TPF induction therapy + cisplatin/5-fluorouracil with concomitant RT with or without cetuximab (Erbitux®) in patients with squamous cell carcinoma of the head and neck (the AVAPO trial)	SS Giovanni and Paolo Hospital (Associazione Volontari Assistenza Pazienti Oncologia: AVAPO)	Adriano Paccagnella, PI, SS Giovanni and Paolo Hospital, Venice, Italy	Italy, Multicenter	350
7 EORTC 24061: Randomized phase II feasibility study of cetuximab (Erbitux®) combined with 4 cycles of TPF followed by platinum-based chemoradiation strategies	European Organisation for Research and Treatment of Cancer (EORTC) Head and Neck Group	Jan Baptiste Vermorken (Study coordinator, Universitair Ziekenhuis Antwerpen, Edegem, Belgium)	EU, multicentre	55
8 Organ preservation trial for advanced primary untreated squamous cell carcinoma of the phar-ynx and larynx (Stage III/IV)	Dept of ORL and Head and Neck Surgery, University Clinic – Frankfurt, Frankfurt, Germany	Rainald Knecht (Chief Investigator, University Clinic – Frankfurt, Frankfurt, Germany) Volker Budach (Chief Co-Investigator, Klinik und Poliklinik fuer Strahlentherapie, University Clinic – Berlin, Berlin, Germany)	Germany, multicenter	328

Design/disease stage	Treatments[a]	Primary objective	Year started
Randomized, open label, LA SCCHN (only N2/N3)	2 cycles of TPF ICT vs no induction CT followed by RT plus docetaxel/5-FU and oral hydroxyurea	OS	2004
Randomized, open label LA SCCHN	Arm A: 3 cycles of TPF ICT followed by CCRT; splitting of the arm: Arm A1 (poor response during induction): docetaxel weekly for 4 weeks + RT with accelerated concomitant boost Arm A2 (good response during induction): carboplatin + RT Arm B: no induction CT; cisplatin + RT	OS	2004
Randomized, open label, parallel group LA SCC larynx	3 cycles of TPF followed by RT plus either 3-wkly cisplatin x 3 or cetuximab (loading dose then wkly) for 8 cycles (only in patients with >50% response to TPF)	Laryngeal preservation rate	2005
Open label Recurrent/metastatic SCCHN	IV docetaxel plus IV bortezomib on Days 1 and 8, every 4 wks	ORR	2005
Open label LA SCCHN	RT once daily, 5 days per wk for 8 wks plus IV docetaxel once per wk for 8 wks plus IV bevacizumab every 2 wks for up to 1 year	TTP	2005
Randomized, parallel group LA SCCHN	Arm A: induction chemotherapy (TPF every 3 wks for 3 cycles) then cisplatin + 5-fluororacil + RT ± cetuximab Arm B: cisplatin + 5-fluororacil + RT ± cetuximab (no induction CT)	OS	2007
Randomized, parallel group LA SCCHN	Arm A: induction with TPF (2 or 4 cycles depending on progression) followed by CCRT with wkly cisplatin Arm B: induction with TPF (2 or 4 cycles depending on progression) followed by CCRT with wkly carboplatin Both arms receive weekly cetuximab throughout	Feasibility of delivery of the regimens based on ≥80% of the per-protocol dose intensity of RT, platinum and cetuximab during the CCRT phase	Projected: Q2 2008
Open label, randomized, phase III LA SCCHN	Group 1: TPF (every 3 wks for 3 cycles) followed by accelerated RT with concomitant boost + cetuximab Group 2: no induction CT; accelerated RT with concomitant boost + cetuximab	OS	Projected: Q2 2008

(Continued)

Table 4 (*Contiuned*)

Name	Sponsor/ collaborator	Primary investigator	Primary site	Planned patient no
Pharma-sponsored clinical trials (combining docetaxel with biologics)				
9 Randomized phase II study of docetaxel in combination with vandetanib (Zactima®, ZD6474) in patients with LA squamous cell carcinoma of the head and neck	DFCI Brigham and Women's Hospital (BWH) Beth Israel Deaconess Medical Center (BIDMC) Massachusetts General Hospital (MGH) AstraZeneca	Robert Haddad (PI, DFCI, Harvard Medical School, Boston, Massachusetts, USA)	US, multicenter	72
10 Phase II trial of docetaxel, cetuximab (C225; Erbitux®), and cisplatin followed by radiation, cetuximab, and cisplatin in LA head and neck cancer	University of Pittsburgh Bristol-Myers Squibb (BMS)	Athanassios (Ethan) Argiris (PI, University of Pittsburgh, Pittsburgh, PA, USA)	University of Pittsburgh, Pittsburgh, PA, USA	40
11 A randomized, open-label, controlled, phase II trial of combination chemotherapy with or without panitumumab (Vectibix®) as first-line treatment of subjects with metastatic or recurrent head and neck cancer, and cross-over second-line pani-tumumab monotherapy of patients who fail the combination chemotherapy (the PARTNER trial: Panitumumab Added to Regimen for Treatment of head and Neck cancer – Evaluation of Response)	Amgen	Company-coordinated trial	Amgen Research Site, Paducah, KY, USA	150
12 Phase I evaluation of erlotinib (Tarceva®) and docetaxel with concomitant boost radiation for locoregionally advanced squamous cell carci-noma of the head and neck	University of Texas – M.D. Anderson Cancer Center Genentech (Also supported – but not sponsored – by sanofi-aventis)	Bonnie S. Glisson (PI, M.D. Anderson Cancer Center, Houston, TX, USA)	M.D. Ander-son Cancer Center, Houston, TX, USA	24
13 Phase I sequential therapy: Panitumumab (Vectibix®) (P)-TPF plus P-CT chemoradio-therapy DFCI Trial #: 05–401	DFCI Amgen	Marshall Posner, Robert Haddad (co-PIs, DFCI, Boston, MA, USA)	US, single center	24
14 GSTTC: one-step four-arm randomized trial of TPF induction chemotherapy followed by PF + cetuximab (Erbitux®) in patients with squamous cell carcinoma of the head and neck	Gruppo di Studio sui Tumori della Testa e Collo (GSTTC) Merck KGaA	Adriano Paccagnella, PI, Venice, Italy	Italy, multi-center	300
15 DFCI: TPF plus cetuximab (Erbitux®) (TPF-3) phase I trial of sequential chemotherapy and cetuximab DFCI Trial #: 06–128	DFCI BMS	Robert Haddad (PI, DFCI, Harvard Medical School, Boston, MA, USA)	US, multi-center	30–40

Docetaxel in combination with the topoisomerase I inhibitor irinotecan (Tax-Iri) has demonstrated activity in M/R SCCHN, with acceptable and predominantly gastrointestinal side effects (Argiris et al 2005). This combination is of interest as the 2 drugs have partially non-overlapping side effect profiles, and there is preclinical evidence of synergistic activity, with phase I studies demonstrating that both drugs can be given safely in a weekly schedule. In this study, patients were divided into 2 cohorts: those who were chemotherapy-naïve (n = 17) and those who had been previously treated with 1 chemotherapy regimen (n = 37). The study regimen consisted of docetaxel 35 mg/m^2 plus irinotecan 60 mg/m^2 on Days 1 and 8, every 3 weeks, until disease progression or limiting toxicity.

With response data available for 47 patients, there were 4 objective PRs in 17 chemotherapy-naïve patients (24%), and 1 PR in 30 pretreated patients (3%). Median PFS and OS durations were longer among chemotherapy-naïve patients

Design/disease stage	Treatments[a]	Primary objective	Year started
Phase II, randomized, open label, parallel group LA SCCHN	Docetaxel once every 3 wks plus vandetanib once daily	Response rate	March 2007
Phase II, open label, non-randomized, parallel group LA SCCHN	Docetaxel plus cetuximab plus cisplatin followed by RT + cetuximab + cisplatin	Objective response rate	2005
Phase II, randomized, open label, parallel group Recurrent/metastatic SCCHN	Docetaxel plus cisplatin ± panitumumab	PFS	2007
Phase I, non-randomized, open label	Docetaxel 15 or 20 mg/m^2 on Days 1, 8, 15, and 22 plus oral erlotinib 100, 125, or 150 mg on all other days the patient is not receiving docetaxel + RT (includes concomitant boost)	Maximum tolerated dose of docetaxel + erlotinib during concomitant boost radiation	2005
Phase I, non-randomized, open label	Docetaxel + cisplatin + 5-FU + panitumumab, every 3 wks for 3 cycles, followed by panitumumab + carboplatin + paclitaxel with daily RT	Maximum tolerated dose of docetaxel and panitumumab in the delivered schema	2007
Randomized, parallel group	Arm A: TPF induction chemotherapy then either PF or cetuximab Arm B: no induction therapy, followed by either PF or cetuximab	ORR; TTP	Projected: 2008
Phase I, non-randomized, open label	TPF + cetuximab followed by platinum-based chemo-radiotherapy	Maximum tolerated dose of docetaxel and cetuximab in the delivered schema	2007

Abbreviations: 5-FU, 5-fluororoucil; IV, intravenous; LA, locally advanced; ORR, overall response rate; PFS, progression-free survival; PI, principal investigator; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; TPF, docetaxel + cisplatin + 5-fluorouracil; TTP, time to progression.

(3.2 and 9.8 months, respectively) compared with pretreated patients (1.8 and 5.2 months, respectively). The main AEs (51 evaluable patients) included neutropenia (grade 3, 8%; grade 4, 10%), fatigue (grade 3, 16%), anorexia (grade 3, 8%; grade 4, 4%), diarrhea (grade 3, 24%; grade 4, 2%), stomatitis (grade 3, 2%), vomiting (grade 3, 4%; grade 4, 2%), febrile neutropenia (4%), neutropenic infection (grade 3, 2%; grade 4, 4%), dyspnea (grade 3, 2%; grade 4, 2%), and creatinine abnormality (grade 3, 2%; grade 4, 4%).

Docetaxel has also been combined with 5-FU (TF) for the treatment of locally recurrent and/or metastatic SCCHN (Genet et al 2004). Patients in this study were divided into pretreated (n = 20) and treatment-naïve (n = 43) groups, and received docetaxel 75 mg/m^2 Day 1 plus 5-FU 1000 mg/m^2 Days 1–5, every 3 weeks. A total of 59 patients (94%) had received prior RT. The ORR was 20.6%: 25.0% for pretreated vs 18.6% for treatment-naïve patients. Overall, the major grade 3/4 AEs included

Table 5 Docetaxel–cisplatin as a "core" combination for the treatment of metastatic or recurrent squamous cell carcinoma of the head and neck

Reference	Regimen	Patients, n	Complete RR, %	ORR, %	OS, %		Median OS, months
					1-year	2-year	
Gedlicka et al (2002)	Docetaxel 75 mg/m^2 D1	38	17.5	52.5	50	9	11 (range 1–30)
	Cisplatin 75 mg/m^2 D1						
	q3w to ≤6 cycles						
Yabuuchi et al (2003)	Docetaxel 60 mg/m^2	17	–	71	–	–	–
	Cisplatin 70 mg/m^2						
Hehr et al (2005)	Docetaxel 50 mg/m^2 D1	39	–	80	–	20	10
	Cisplatin 15 mg/m^2 D2-5						
	q3w for 3 cycles + RT 2.0 Gy once daily D8–12, 15–19, 29–33, 36-40						
Guntinas-Lichius et al (2006)	Docetaxel 35 mg/m^2	21	0	42	45	–	10.7
	Cisplatin 25 mg/m^2						(95% CI: 6.4–15.0)
	D1, 8, 15, q4w						
Baghi et al (2006)	Docetaxel 75 mg/m^2 D1	24	25	42	–	–	13 (range 6–48)
	Cisplatin 100 mg/m^2 D1						
	5-fluorouracil 1000 mg/m^2 D1–4						
	q3w to ≤3 cycles						
Peyrade et al (2006)	Docetaxel 75 mg/m^2 D1	40	15	63	–	–	13
	Cisplatin 75 mg/m^2 D1						
	5-fluorouracil 750 mg/m^2 D2–5 q3w						

Abbreviations: CI, confidence interval; ORR, overall response rate; OS, overall survival; q3w, every 3 weeks ; q4w, every 4 weeks ; RR, response rate; RT, radiotherapy.

neutropenia (66.6%), febrile neutropenia (31.7%), and mucositis (31.7%). After the first 20 patients were enrolled, the dose of 5-FU was reduced to 750 mg/m^2 due to toxicity; thereafter, the rate of febrile neutropenia fell from 40.0% to 27.9% and that of mucositis fell from 55.0% to 20.9% (Genet et al 2004).

Docetaxel triplet therapy other than TPF

Triplet therapy using variations on the "standard" TPF regimen have also been investigated in several recent trials. The combination of docetaxel 50 to 60 mg/m^2 and cisplatin 70 mg/m^2 Day 1, plus the oral fluoropyrimidine S-1 40 to 80 mg/m^2/day Days 1–14, every 4 weeks (the TPS regimen), showed promising antitumor activity in a phase I dose-escalation study (Tahara et al 2007). A median of 3 cycles

(range 1–6) of treatment was administered to 22 patients with LA or recurrent/metastatic SCCHN; CR was observed in 3 patients (1 with locally recurrent disease, 2 with meta-static disease) and PR in 11 patients (7 with locally recurrent disease, 4 with metastatic disease). The ORR was 64%.

Of note, the combination of docetaxel (80 mg/m^2 Day 15), cisplatin (80 mg/m^2 Day 1) and the fluoropyrimidine gem-citabine (1100 mg/m^2 Days 1 and 15) (TPG) every 4 weeks showed modest activity in 21 patients with relapsed or metastatic SCCHN (Kouroussis et al 2005), with an ORR of 33% (95% CI: 22.4–55.1). The median duration of response was 8.9 months, with a median TTP of 6 months and an estimated median OS of 8.1 months. Toxicity was manageable, and included febrile neutropenia (4%), grade 3/4 neutropenia (41%), grade 3 anemia, mucositis,

asthenia, and vomiting (4% each). Out of 107 cycles given cumulatively to the entire cohort during this study, a total of 19 cycles (18%) were delayed, 16 cycles (15%) were associated with dose reductions, and 60 cycles (56%) required granulocyte colony-stimulating factor (G-CSF) support. A phase II study of doublet therapy using docetaxel 75 mg/m^2 Day 8 plus gemcitabine 1000 mg/m^2 Days 1 and 8 (TG or GemDoc) every 3 weeks for 6 cycles in patients with recurrent and/or metastatic SCCHN, also showed a high incidence of grade 3/4 neutropenia (18/40 patients [45%]) (Labourey et al 2007).

In view of the more favorable safety profile of Cb compared with cisplatin, a docetaxel and Cb combination has also been investigated. A total of 96 patients with metastatic or recurrent SCCHN participated in this study, and the TCb combination was associated with a longer median survival duration compared with Pacli-Cb doublet (37 months vs 10.9 months, respectively) (Bickmann et al 2006). Patients enrolled in this trial received either weekly docetaxel 35 mg/m^2 plus Cb AUC 2.0 or paclitaxel 100 mg/m^2 plus Cb AUC 2.0, for a maximum of 6 cycles. CR was seen in 25.0% of patients receiving docetaxel, compared with 9.6% receiving paclitaxel, while PR was seen in 34.1% of patients receiving docetaxel vs 38.5% receiving paclitaxel. These data corresponded to an ORR of 59.1% for TCb and 48.1% for Pacli-Cb. Leukopenia was the most frequent toxicity, with grade 1–3 leukopenia occurring in 12.0%, 27.0%, and 15.0% of paclitaxel recipients, respectively, and 25.0%, 23.0%, and 16.0% of docetaxel recipients, respectively.

Another triple-therapy combination phase II study investigated docetaxel, Cb, and the oral fluoropyrimidine capecitabine (Xeloda®) (TCb-X) in 21 patients with recurrent (n = 15) or metastatic (n = 6) SCCHN (Kattan et al 2005). There was 1 CR and 8 PRs, for an ORR of 43%, which was comparable with that reported in the literature. The median TTP was 4.2 months. It is notable that this regimen was very well tolerated, with grade 3/4 anemia and thrombocytopenia reported in only 2 patients each (<10% of the cohort).

Role of docetaxel in systemic chemotherapy in the recurrent/ metastatic disease setting

Summarizing the data presented in the sections above, docetaxel-based chemotherapy, whether as single-agent, or more importantly as part of doublet- or triplet-chemotherapy regimens, shows considerable activity in the recurrent/ metastatic SCCHN setting. Nevertheless, this disease has been considered an extremely difficult one in which to provide truly effective treatment, a fact reflected in poor rates of long-term survival. Docetaxel-based regimens are associated with promising OS and PFS, indicating that further investigation to improve outcomes with docetaxel-containing templates is warranted.

Future directions

It is likely that the future of docetaxel in the treatment of SCCHN lies with TPF, a combination that can be used as the platform for curative-intent ICT in LA disease. Evolution of this triple-drug regimen toward one that includes platinum agents and oral fluoropyrimidines other than cisplatin and 5-FU, as well as molecularly targeted therapies, is the subject of recent investigation. Biologic agents as "add-ons" to TPF are of particular interest; ongoing trials focusing on these are summarized in Table 4.

The epidermal growth factor receptor (EGFR) in particular, plays an important role in many epithelial cancer types, including that of the head and neck. Overexpression of this receptor is associated with increased tumor growth, metastasis, resistance to chemotherapeutic agents, and poor prognosis (Jones et al 2006). Molecules targeting the EGFR, such as erlotinib, gefitinib, and cetuximab, form an important component of novel treatment approaches in combination with docetaxel for the treatment of SCCHN. In this section, a brief overview of the potential to combine these novel targeted agents with TPF is discussed.

Erlotinib

Several recent phase I and II studies have investigated the combination of docetaxel and the EGFR tyrosine kinase inhibitor (TKI) erlotinib. The feasibility of combining weekly docetaxel (15–20 mg/m^2) with daily erlotinib (50–100 mg), and concomitantly delivered RT (1.8 Gy/day to 70.2 Gy) was demonstrated in a phase I study in patients with LA stage III-IVb SCCHN (Savvides et al 2006). Following docetaxel–erlotinib CCRT, best response observed was CR in 15/18 patients (83%); 2 patients were not evaluable and 1 died during the study.

The activity of docetaxel, erlotinib, and cisplatin combination chemotherapy was also encouraging in a phase II trial of 37 patients with metastatic or recurrent SCCHN (Kim et al 2006). Patients received docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2, every 3 weeks, with daily erlotinib 150 mg; G-CSF support was also administered. Treatment was associated with CR in 3 patients, PR in 18 patients, and SD in 8 patients,

corresponding to an ORR of 66% and an impressive disease control rate of 91%. Treatment was well tolerated, with the main AEs being grade 3/4 neutropenia (14%, including 5% with febrile neutropenia), grade 4 diarrhea (3%), and grade 3 rash (5% patients).

Gefitinib

Another EGFR TKI, gefitinib, has been investigated in combination with docetaxel-based regimens for the treatment of SCCHN. The addition of gefitinib to the well-established TP combination was investigated in a phase II trial in 23 patients with recurrent /metastatic SCCHN (Belon et al 2005). Among 16 patients eligible for efficacy analysis, after a median of 4 cycles of TP (75 mg/m^2 each, every 3 weeks) and 71 days (range 7–244) of gefitinib therapy (250 mg/day), there were 6 CRs (37.5%) and 4 PRs (25.0%), corresponding to an ORR of 62.5% (95% CI: 35.4–84.8). The disease control rate was 75.0% (95% CI: 47.6–92.7). In this trial, the median PFS of 5.1 months (95% CI: 2.0–7.1) was of interest, given that the expected OS of patients with recurrent and/or metastatic SCCHN is only usually 6 months (Belon et al 2005). All 17 patients were eligible for safety analysis, with grade 3/4 AEs including neutropenia (41.2% of patients, including 23.5% with febrile neutropenia), anemia (17.7%), asthenia (11.8%), and diarrhea, vomiting, anorexia, and leukopenia (5.9% each).

Cetuximab (C225)

Cetuximab (Erbitux®), a chimeric IgG1 monoclonal antibody directed against the extracellular domain of the EGFR, has been investigated in combination with RT and as part of a docetaxel-based induction regimen for the management of LA SCCHN.

In a phase III study that compared RT alone with cetuximab plus RT, the combination of cetuximab plus RT improved LRC and increased the OS of patients with LA SCCHN vs RT alone (49 months vs 29.3 months, respectively); however, severe toxicity in the form of acneiform rashes and infusion reactions – occasionally life-threatening – occurred in the group receiving the cetuximab/RT combination, but not in the group receiving RT alone (Bonner et al 2006).

In a phase II study, 21 previously untreated patients with stage III/IV (M1) or selected stage II (base of tongue, hypopharynx or nasopharynx) SCCHN received docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 Day 1, plus cetuximab 400 mg/m^2 loading dose Day 1 then 250 mg/m^2 on Days 1, 8, and 15, every 3 weeks for 3 cycles (the TP-E regimen)

(Argiris et al 2007). Patients went on to receive concomitant bio-chemoradiotherapy as RT (2 Gy/day to 70 Gy) with concurrent weekly cisplatin (30 mg/m^2) and cetuximab (250 mg/m^2), followed by cetuximab maintenance therapy for 6 months. The ORR among 16 evaluable patients was 94.0% (CR: 12.5%; PR: 75.0%; SD: 6.25%). Twenty patients were eligible for the safety analysis; serious AEs included neutropenia (grade 3, 20%; grade 4, 35%), anemia (grade 3, 5%), thrombocytopenia (grade 3, 5%), hypomagnesemia (grade 3, 10%; grade 4, 5%), rash, fatigue, and diarrhea (5%, grade 3 for each). One patient experienced grade 3 infusion reaction during the first administration of cetuximab and was withdrawn from the study.

Recently, a retrospective efficacy analysis showed that the combination of TP–5-FU induction therapy with cetuximab is feasible, resulting in a primary site ORR of 71% (CR: 14%; PR: 57%) in 21 consecutively treated patients with LA SCCHN (Kuperman et al 2007). The ORR at regional nodes was 83% (CR: 39%; PR: 44%). Neutropenic infection and grade 3/4 infusion reactions were observed in 19% of patients each, and grade 3/4 sepsis in 5%.

It should be noted that the combination of paclitaxel with cetuximab has been shown to result in high levels of skin toxicity (grade 3 or 4 in 24% of patients) (Hitt et al 2007). As there are currently only a few preliminary studies docetaxel and cetuximab, it is not possible to predict at this time what levels of skin toxicities may occur with this combination.

RNA-interfering molecules

Novel approaches to target the EGFR in cancer include the diminution of EGFR expression using interfering molecules and antibodies; in fact, several recent preclinical studies have investigated the potential of EGFR in pre-transcriptional inhibition of the EGFR gene to enhance the activity of conventional chemotherapeutic agents (Niwa et al 2003; Nozawa et al 2006). The addition of EGFR small interfering RNA (siRNA) to cisplatin, 5-FU, and docetaxel enhanced chemosensitivity (Nozawa et al 2006). The siRNA acts to efficiently downregulate EGFR expression, inhibiting cell growth and enhancing chemosensitivity to TP therapy, resulting in a significant increase in apoptosis. In an SCCHN xenograft model, EGFR siRNA delivered by atelocollagen enhanced the antitumor activity of cisplatin, suggesting that this combination may improve chemotherapeutic efficacy in the clinic. Similar enhancement of docetaxel activity was observed in SCCHN cell lines and xenografts treated with an EGFR antisense oligonucleotide targeting region 760–779 of the EGFR mRNA

(Niwa et al 2003). Increased cytotoxicity was observed with TPF compared with EGFR sense oligonucleotide plus docetaxel (or docetaxel alone). Furthermore, addition of the anti-EGFR antibody to TPF significantly reduced the mouse xenograft tumor volumes. Of note, the TPF triplet plus an anti-EGFR antibody achieved complete remissions lasting up to 6 weeks in another preclinical study in mouse SCCHN xenografts (Knecht et al 2003).

In view of the promising activity of novel biologic and targeted agents when used in combination with docetaxel-based chemotherapy, several trials investigating the incorporation of targeted therapies, including erlotinib (Tarceva®), cetuximab, bortezomib (Velcade®), panitumumab (Vectibix®), vandetanib (ZD6474; Zactima®), and bevacizumab (Avastin®), into docetaxel-based regimens are currently underway (Table 4). The results from these clinical trials are eagerly anticipated and are predicted to improve outcomes in patients with SCCHN in both the LA and recurrent or metastatic setting.

Conclusions

Docetaxel is an agent with proven activity in the treatment of SCCHN. The pivotal TAX 323 and TAX 324 studies have recently established TPF as the most effective combination regimen for ICT, if the latter is chosen as the basis of a multidisciplinary program for the treatment of LA SCCHN. Future directions for docetaxel-based therapies include combination with other chemotherapeutic agents and novel biologic therapies – most notably agents targeted against the EGFR – and modification of CCRT regimens. As an increasing number of targeted therapies become available for clinical trials (and eventually at the practicing oncologist's office), we can hope to see more active combinations in SCCHN; indeed, there may be added benefit from using such combinations as part of ICT regimens, integrated into the RT part of the sequential therapy regimen, or even as maintenance after the successful delivery of the local/regional component of the regimen (in complete responders). There is currently a paucity of data on molecular endpoints that would be of prognostic and/or predictive value relevant to the use of TPF; such data could help stratify patients (according to disease site, stage, human papilloma virus tissue typing status, for example) who would benefit from induction therapy vs those who may not. Secondary analysis of existing study data (eg, TAX 324) may provide some insight in this regard, but future studies should include appropriate endpoints to be prospectively investigated.

Promising results from ongoing studies with docetaxel-based treatments in SCCHN indicate that these regimens are poised to foster further improvement in patient outcomes, especially in LA disease, which has the potential to become a widely curable disease. Finally, refinements in current treatment strategies incorporating docetaxel could increasingly prove clinical usefulness for the management of SCCHN in the metastatic or recurrent disease setting, which has been marred, historically, by poor outcomes.

Acknowledgments

Disclosures

Abbreviations
AE, adverse event; AUC, area under the curve; Cb, carboplatin(um); CCRT; concomitant chemoradiotherapy; CEP, cisplatin, epirubicin, and paclitaxel; CI; confidence interval; CR, complete response; DFS, disease-free survival; DMs, distant metastases; EGFR, epidermal growth factor receptor; EMEA; European Medicines Agency; EORTC, European Organization for Research and Treatment of Cancer; FDA, Food and Drug Administration; 5-FU, 5-fluorouracil; G-CSF, granulocyte colony-stimulating factor; GORTEC, Groupe d'Oncologie Radiotherapie Tete et Cou; HeCOG, Hellenic Cooperative Oncology Group; HPV, human papilloma virus; HR, hazard ratio; ICT, induction chemotherapy; LA, locally advanced; LRC, locoregional control; MACH-NC, Meta-analysis of Chemotherapy in Head and Neck Cancer; M/R, metastatic or recurrent; NCI, National Cancer Institute; NPC, nasopharyngeal carcinoma; ORR, overall response rate; OS, overall survival; Pacli, paclitaxel; pCR, pathologic complete response; PF, cisplatin-5-fluorouracil; PFS, progression-free survival; PORT, postoperative radiotherapy; PR, partial response; PS, performance status; PSS-HN, Performance Status Scale for Head and Neck patients; RTOG; Radiation Therapy Oncology Group; QLQ, Quality of Life Global Health Questionnaire; QoL, quality of life; RR, response rate; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; SEER, Surveillance Epidemiology and End Results; siRNA, small interfering RNA; SWOG, Southwest Oncology Group; TCb, docetaxel (Taxotere®)-carboplatin; TKI, tyrosine kinase inhibitor; TP, docetaxel (Taxotere®)-cisplatin; TPF, docetaxel

(Taxotere®)-cisplatin-5-fluorouracil; TTF, time to treatment failure; TTP, time to progression; UICC/AJCC, Union Internationale Contre le Cancer/American Joint Committee on Cancer; WHO, World Health Organization.

References

Adelstein DJ, Leblanc M. 2006. Does induction chemotherapy have a role in the management of locoregionally advanced squamous cell head and neck cancer? *J Clin Oncol*, 24:2624–8.

Adelstein DJ, Saxton JP, Lavertu P, et al. 2002. Maximizing local control and organ preservation in stage IV squamous cell head and neck cancer with hyperfractionated radiation and concurrent chemotherapy. *J Clin Oncol*, 20:1405–10.

Airoldi M, Cattel L, Marchionatti S, et al. 2003. Docetaxel and vinorelbine in recurrent head and neck cancer: pharmacokinetic and clinical results. *Am J Clin Oncol*, 26:378–81.

Al-Sarraf M, LeBlanc M, Giri PG, et al. 1998. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol*, 16:1310–7.

Argiris A, Goldwasser A, Brockstein B, et al. 2005. Weekly docetaxel (D) and irinotecan (I) in patients (pts) with recurrence of metastatic head and neck cancer (HNC): a phase II trial of the Eastern Cooperative Oncology Group (ECOG) [abstract]. *J Clin Oncol*, 23(16S): Abstract 5528.

Argiris A, Karamouzis MV, Heron DE, et al. 2007. Phase II trial of docetaxel (T), cisplatin (P), and cetuximab (E) followed by concurrent radiation (RT), P, and E in locally advanced head and neck squamous cell carcinoma (HNSCC). *J Clin Oncol*, 25(18S):Abstract 6051.

Baghi M, Hambek M, Wagenblast J, et al. 2006. A phase II trial of docetaxel, cisplatin and 5-fluorouracil in patients with recurrent squamous cell carcinoma of the head and neck (SCCHN). *Anticancer Res*, 26:585–90.

Barone C, Grillo R, Dongiovanni D, et al. 2008. Induction chemotherapy followed by concurrent chemoradiotherapy in advanced head and neck squamous cell carcinoma. *Anticancer Res,* 28:1285–91.

Belon J, Irigoyen A, Rodriguez I, et al. 2005. Preliminary results of a phase II study to evaluate gefitinib combined with docetaxel and cisplatin in patients with recurrent and/or metastatic squamous-cell carcinoma of the head and neck [abstract]. *J Clin Oncol*, 23(16S):Abstract 5563.

Bickmann A, Holzgraefe M, Wolf M, et al. 2006. Combination therapy of docetaxel, carboplatin or paclitaxel, carboplatin for patients with metastatic/recurrent carcinoma of the head and neck (SCCHN) [abstract]. *J Clin Oncol*, 24(18S):Abstract 557).

Bonner JA, Harari PM, Giralt J, et al. 2006. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*, 354:567–78.

Bouillet T, Nizri D, Zawadi A, et al. 2007. A randomized phase II study of concomitant CT (docetaxel ± cisplatin) and (RT) in first-line treatment of locally advanced head and neck cancer (LAHNC) [abstract]. *J Clin Oncol*, 25(18S):Abstract 6047.

Calais G, Pointreau Y, Alfonsi M, et al. 2006. Randomized phase III trial comparing induction chemotherapy using cisplatin (P) fluorouracil (F) with or without docetaxel (T) for organ preservation in hypopharynx and larynx cancer. Preliminary results of GORTEC 2000–01 [abstract]. *J Clin Oncol*, 24(18S):Abstract 5506.

ClinicalStudyResults.org. 2008. [online]. Accessed 8 May 2008. URL: http://www.clinicalstudyresults.org/documents/company-study_1730_0.pdf.

Clinicaltrials.gov. 2008. [online]. Accessed 8 May 2008. URL: http://Clinicaltrials.gov/.

Colevas AD, Busse PM, Norris CM, et al. 1998. Induction chemotherapy with docetaxel, cisplatin, fluorouracil, and leucovorin for squamous cell carcinoma of the head and neck: a phase I/II trial. *J Clin Oncol*, 16:1331–9.

Colevas AD, Norris CM, Tishler RB, et al. 1999. Phase II trial of docetaxel, cisplatin, fluorouracil and leucovorin as induction for squamous cell carcinoma of the head and neck. *J Clin Oncol*, 17:3503–11.

Colevas AD, Norris CM, Tishler RB, et al. 2002. Phase I/II trial of outpatient docetaxel cisplatin, 5-fluorouracil, leucovorin (opTPFL) as induction for squamous cell carcinoma of the head and neck (SCCHN). *Am J Clin Oncol*, 25:153–9.

Department of Veterans Affairs Laryngeal Cancer Study Group. 1991. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med*, 324:1685–90.

European Medicines Agency. 2007. Document reference EMEA/479200/2007 [online]. Accessed 8 May 2008. URL: http://www.emea.europa.eu/pdfs/human/press/pr/47920007en.pdf.

Feenstra J, Vermeer RJ, Stricker BH. 2000. Mesenteric venous thrombosis attributed to docetaxel. *Am J Clin Oncol*, 23:353–4.

Forastiere AA, Goepfert H, Maor M, et al. 2003. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*, 349:2091–8.

Fountzilas G, Tolis C, Kalogera-Fountzila A, et al. 2005a. Induction chemotherapy with cisplatin, epirubicin, and paclitaxel (CEP), followed by concomitant radiotherapy and weekly paclitaxel for the management of locally advanced nasopharyngeal carcinoma. A Hellenic Cooperative Oncology Group phase II study. *Strahlenther Onkol*, 181:223–30.

Fountzilas G, Tolis C, Kalogera-Fountzila A, et al. 2005b. Paclitaxel, cisplatin, leucovorin, and continuous infusion fluorouracil followed by concomitant chemoradiotherapy for locally advanced squamous cell carcinoma of the head and neck: a Hellenic Cooperative Oncology Group Phase II Study. *Med Oncol*, 22:269–79.

Gedlicka C, Formanek M, Slezer E, et al. 2002. Phase II study with docetaxel and cisplatin in the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Oncology*, 63:145–50.

Genet D, Cupissol D, Calais G, et al. 2004. Docetaxel plus 5-fluorouracil in locally recurrent and/or metastatic squamous cell carcinoma of the head and neck: a phase II multicenter study. *Am J Clin Oncol*, 27:472–6.

Ghi MG, Paccagnella A, Koussis H, et al. 2006. Randomized phase II-III trial of concomitant CT/RT versus TPF followed by concomitant CT/RT in locally advanced squamous cell carcinoma of the head and neck (LASCCHN). Results of the phase II part of the study [abstract]. *Ann Oncol*, 17(Suppl 9):Abstract 5730.

Greene FL, Page DL, Fleming ID. 2002. American Joint Committee on Cancer (AJCC). AJCC cancer staging manual. 6th ed. New York: Springer-Verlag.

Guardiola E, Peyrade F, Chaigneua L, et al. 2004. Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. *Eur J Cancer*, 40:2071–6.

Guntinas-Lichius O, Appenrodt S, Veelken F, et al. 2006. Phase II study of weekly docetaxel and cisplatin in patients with advanced recurrent and metastatic head and neck cancer. *Laryngoscope*, 116:613–8.

Hehr T, Classen J, Belka C, et al. 2005. Docetaxel/cisplatin alternating with re-irradiation in recurrent head and neck cancer [abstract]. *J Clin Oncol*, 23(16S):Abstract 5540.

Hitt R, Amador ML, Quintela-Fandino M, et al. 2006a. Weekly docetaxel in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Cancer*, 106:106–11.

Hitt R, Hornedo J, Colomer R, et al. 1995. A phase I/II study of paclitaxel plus cisplatin as first-line therapy for head and neck cancers: preliminary results. *Semin Oncol*, 22(Suppl 15):50–4.

Hitt R, Grau J, Lopez-Pousa A, et al. 2006b. Randomized phase II/III clinical trial of induction chemotherapy with either cisplatin/5-fluorouracil (PF) or docetaxel/cisplatin/5-fluorouracil (TPF) followed by chemoradiotherapy (CRT) vs CRT alone for patients (pts) with unresectable locally advanced head and neck cancer (LAHNC) [abstract]. *J Clin Oncol*, 24(18S):Abstract 5515.

Hitt R, Irigoyen A, Nuńez J, et al. 2007. Phase II study of combination cetuximab and weekly paclitaxel in patients with metastatic/recurrant squamous cell carcinoma of the head and neck (SCCHN):Spanish Head and Neck Cancer Group (TTCC). *J Clin Oncol*, 25:6012.

Hitt R, López-Pousa A, Martínez-Trufero J, et al. 2005. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol,* 23:8636–45. Erratum in: *J Clin Oncol*, 2006; 24:1015.

Hitt R, Paz-Ares L, Brandáriz A, et al. 2002. Induction chemotherapy with paclitaxel, cisplatin and 5-fluorouracil for squamous cell carcinoma of the head and neck: long-term results of a phase II trial. *Ann Oncol*, 13:1665–73.

Hoffman H, Cooper JS, Weber R, et al. 2004. Changing patterns of practice in the management of nasopharynx carcinoma (NPC): analysis of the National Cancer Database (NCDB) [abstract]. *J Clin Oncol*, 22(14S): Abstract 5507.

Irish J, Lee A. 2005. Head and Neck cancer; International Union Against Cancer (IUAC). Manual of Clinical Oncology. 8th ed. San Francisco: John Wiley and Sons, Inc.

Janinis J, Papadakou M, Panagos G, et al. 2001. Sequential chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil in patients with locally advanced head and neck cancer. *Am J Clin Oncol*, 24:227–31.

Johnson FM, Garden A, Palmer JL, et al. 2004. A Phase II study of docetaxel and carboplatin as neoadjuvant therapy for nasopharyngeal carcinoma with early T status and advanced N status. *Cancer*, 100:991–8.

Jones HE, Gee JM, Hutcheson IR, et al. 2006. Growth factor receptor interplay and resistance in cancer. *Endocr Relat Cancer*, 13(Suppl 1): S45–51.

Kandil MS, Alnasser HS, Bandey SA, et al. 2007. Phase II neoadjuvant docetaxel/cisplatin followed by concurrent cisplatin/radiotherapy for locally advanced nasopharyngeal cancer [abstract]. *J Clin Oncol*, 25(18S):Abstract 6059.

Katori H, Tsukuda M, Ishitoya J, et al. 2005. Comparison of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (TPF) followed by radiation versus concurrent chemoradiotherapy with TPF in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [abstract]. *J Clin Oncol*, 23(16S): Abstract 5580.

Katori H, Tsukuda M, Watai K. 2006. Comparison of hyperfractionation and conventional fractionation radiotherapy with concurrent docetaxel, cisplatin and 5-fluorouracil (TPF) chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [abstract]. *Ann Oncol*, 17(Suppl 9):Abstract 580PD.

Kattan J, Farhat F, Chahine G, et al. 2005. The triplet of docetaxel, carboplatin and capecitabine in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) [abstract]. *J Clin Oncol*, 23(16S):Abstract 5585.

Kies MS, Garden AS, Holsinger V, et al. 2006. Induction chemotherapy (CT) with weekly paclitaxel, carboplatin, and cetuximab for squamous cell carcinoma of the head and neck (HN) [abstract]. *J Clin Oncol*, 24(18S):Abstract 5520.

Kim ES, Kies MS, Glisson BS, et al. 2006. Phase II study of combination cisplatin, docetaxel and erlotinib in patients with metastatic/recurrent head and neck squamous cell carcinoma (HNSCC) [abstract]. *J Clin Oncol*, 24(18S):Abstract 5521.

Knecht R, Peters S, Solback C, et al. 2003. EGFR antibody-supplemented TPE-chemotherapy. Preclinical investigations to a novel approach for head and neck cancer induction treatment. *Anticancer Res*, 23:4789–95.

Kouroussis C, Androulakis N, Boukovinas J, et al. 2005. Docetaxel, cisplatin and gemcitabine as first line for patients with advanced/ metastatic head and neck cancer [abstract]. *J Clin Oncol*, 23(16S): Abstract 5586.

Koussis H, Scola A, Bergamo F, et al. 2007. Weekly docetaxel as second-line (palliative) chemotherapy in recurrent/metastatic head and neck squamous cell carcinoma (SCCHN) [abstract]. *J Clin Oncol*, 25(18S): Abstract 6067.

Kuperman DI, Nussenbaum B, Thorstad W, et al. 2007. Retrospective analysis of the addition of cetuximab to induction chemotherapy (IC) with docetaxel, cisplatin, and 5-fluorouracil (TPF-C) for locally advanced squamous cell carcinoma of the head and neck (LA-HNSCC) [abstract]. *J Clin Oncol*, 25(18S):Abstract 6072.

Labourey JL, Cupissol D, Calais G, et al. 2007. Docetaxel plus gemcitabine in recurrent and/or metastatic squamous cell carcinoma of the head and neck: a phase II multicenter study. *Am J Clin Oncol*, 30:278–82.

Laramore GE, Scott CB, al-Sarraf M, et al. 1992. Adjuvant chemotherapy for resectable squamous cell carcinoma of the head and neck: report on Intergroup Study 0034. *Int J Radiat Oncol Biol Phys*, 23:705–13.

Lefebvre JL, Bonneterre J. 1996. Current status of larynx preservation trials. *Curr Opin Oncol*, 8:209–14.

Miller S. 1990. The role of the speech-language pathologist in voice restoration after total laryngectomy. *CA Cancer J Clin*, 40:174–82.

Minea LN, Anghel R, Oprea L, et al. 2007. Concurrent radiation therapy and weekly docetaxel in elderly patients with oropharyngeal carcinoma [abstract]. *J Clin Oncol*, 25(18S):Abstract 16539.

National Cancer Institute. 2008a. A snapshot of head and neck cancer [online]. Accessed 8 February 2008. URL: http://planning.cancer. gov/disease/Head_and_Neck-Snapshot.pdf.

National Cancer Institute. 2008b. SEER Cancer Statistics Review 1995–2005. Table XII-1. Larynx cancer (invasive) [online]. Accessed 8 May 2008. URL: http://seer.cancer.gov/csr/1975_2005/results_merged/ sect_12_larynx.pdf.

National Cancer Institute. 2008c. SEER Cancer Statistics Review 1995–2005. Table XX-1a. Cancer of the oral cavity and pharynx (invasive) [online]. Accessed 8 May 2008. URL: http://seer.cancer. gov/csr/1975_2005/results_merged/sect_20_oral_cavity.pdf.

Nelson GM. 1998. Biology of taste buds and the clinical problem of taste loss. *Anat Rec*, 53:70–8.

Niwa H, Wentzel AL, Li M, et al. 2003. Antitumor effects of epidermal growth factor receptor antisense oligonucleotides in combination with docetaxel in squamous cell carcinoma of the head and neck. *Clin Cancer Res*, 9:5028–35.

Nozawa H, Tadakuma T, Ono T, et al. 2006. Small interfering RNA targeting epidermal growth factor receptor enhances chemosensitivity to cisplatin, 5-fluorouracil and docetaxel in head and neck squamous cell carcinoma. *Cancer Sci*, 97:1115–24.

Paccagnella A, Orlando A, Marchiori C, et al. 1994. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst*, 86:265–72.

Parkin DM, Bray F, Ferlay J, et al. 2005. Global Cancer Statistics, 2002. *CA Cancer J Clin*, 55:74–108.

Peyrade F, Chamorey E, Bozec A, et al. 2006. High efficacy of docetaxel (T) – platinum (P)-5fluoro-uracile (F)- combination (TPF) in heavily pretreated metastatic of locally recurrent head and neck squamous cell carcinoma [abstract]. *Ann Oncol*, 17(Suppl 9):ix183 (Abstract 591P).

Pignon JP, Bourhis J, Domenge C, et al. 2000. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet*, 355:949–55.

Pignon JP, Syz N, Posner M, et al. 2004. Adjusting for patient selection suggests the addition of docetaxel to 5-fluorouracil-cisplatin induction therapy may offer survival benefit in squamous cell cancer of the head and neck. *Anticancer Drugs*, 15:331–40.

Posner MR, Glisson B, Frenette G, et al. 2001. Multicenter phase I-II trial of docetaxel, cisplatin, and fluorouracil induction chemotherapy for patients with locally advanced squamous cell cancer of the head and neck. *J Clin Oncol*, 19:1096–104.

Posner MR, Hershock D, Blajman CR, et al. 2007. Cisplatin and fluoro-uracil alone or with docetaxel in head and neck cancer. *N Engl J Med*, 357:1705–15.

Posner MR, Lefebvre JL. 2003. Docetaxel induction therapy in locally advanced squamous cell carcinoma of the head and neck. *Br J Cancer*, 88:11–7.

Rapidis AD, Trichas M, Stavrinidis E, et al. 2006. Induction chemotherapy followed by concurrent chemoradiation in advanced squamous cell carcinoma of the head and neck: final results from a phase II study with docetaxel, cisplatin and 5-fluorouracil with a four-year follow-up. *Oral Oncol*, 42:675–84.

Remenar E, Van Herpen C, Germa Lluch J, et al. 2006. A randomized phase III multicenter trial of neoadjuvant docetaxel plus cisplatin and 5-fluorouracil (TPF) versus neoadjuvant PF in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN). Final analysis of EORTC 24971 [abstract]. *J Clin Oncol*, 24(18S):Abstract 5516.

Savvides P, Agarwala SS, Greskovich J, et al. 2006. Phase I study of the EGFR tyrosine kinase inhibitor erlotinib in combination with docetaxel and radiation in locally advanced squamous cell cancer of the head and neck (SCCHN) [abstract]. *J Clin Oncol*, 24(18S): Abstract 5545.

Sayed FS, Karim A, Hossain M, et al. 2007. Neoadjuvant chemotherapy with docetaxel and cisplatin followed by concomitant chemoradiotherapy (CT-RT) in the management of locally advanced laryngeal carcinoma [abstract]. *J Clin Oncol*, 25(18S):Abstract 16507.

Schrijvers D, van Herpen C, Kerge J, et al. 2004. Docetaxel, cisplatin and 5-fluorouracil in patients with locally advanced unresectable head and neck cancer: a phase I-II feasibility study. *Ann Oncol*, 15:638–45.

Schrijvers D, Vermorken JB. 2005. Taxanes in the treatment of head and neck cancer. *Curr Opin Oncol*, 17:218–24.

Schuller DE, Metch B, Stein DW, et al. 1988. Preoperative chemotherapy in advanced resectable head and neck cancer: final report of the Southwest Oncology Group. *Laryngoscope*, 98:1205–11.

Seiwert TY, Cohen EEW. 2005. State-of-the-art management of locally advanced head and neck cancer. *Br J Cancer*, 92:1341–8.

Tahara M, Araki K, Kiyota N, et al. 2007. Phase I trial of chemotherapy combination with docetaxel, cisplatin and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer (HNC) [abstract]. *J Clin Oncol*, 25(18S):Abstract 6064.

Tsao AS, Garden AS, Kies MS, et al. 2007. Phase I/II study of docetaxel, cisplatin, and concomitant boost radiation for locally advanced squamous cell cancer of the head and neck. *J Clin Oncol*, 24:4163–9.

Tsukuda M, Mikami Y, Tanigaki Y, et al. 2004. Phase I trial of combined chemotherapy with docetaxel, cisplatin, and 5-fluorouracil for patients with locally advanced squamous cell carcinoma of the head and neck. *Int J Clin Oncol*, 9:161–6.

US Food and Drug Administration. 2007. [online]. Accessed 8 May 2008. URL: http://www.fda.gov/cder/Offices/OODP/whatsnew/dox-etaxel200710.htm.

Vermorken JB, Remenar E, van Herpen C, et al. 2007. Cisplatin, fluoro-uracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med*, 357:1695–704.

Vokes E. 2005. Current treatments and promising investigations in a mul-tidisciplinary setting. *Ann Oncol*, 16(Suppl 6):vi25–30.

Vokes EE, Kies MS, Haraf DJ, et al. 2000. Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. *J Clin Oncol*, 18:1652–61.

Vokes EE, Weichselbaum RR, Lippman SM, et al. 1993. Head and neck cancer. *N Engl J Med*, 328:184–94.

Watanabe A, Taniguchi M, Sasaki S. 2003. Induction chemotherapy with docetaxel, cisplatin, fluorouracil and l-leucovorin for locally advanced head and neck cancers: a modified regimen for Japanese patients. *Anticancer Drugs*, 14:801–7.

Worden FP, Moon J, Samlowski W, et al. 2006. A phase II evaluation of a 3-hour infusion of paclitaxel, cisplatin, and 5-fluorouracil in patients with advanced or recurrent squamous cell carcinoma of the head and neck: Southwest Oncology Group study 0007. *Cancer*, 107:319–27.

Yabuuchi H, Kuroiwa T, Tajima T, et al. 2003. Efficacy of intra-arterial infusion therapy using a combination of cisplatin and docetaxel for recurrent head and neck cancers compared with cisplatin alone. *Clin Oncol* (*R Coll Radiol*), 15:467–72.