Docetaxel in the management of head and neck cancer

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Squamous cell carcinoma of the head and neck is a major health problem, and much effort is being made in the different settings of its presentation. Much of the recent progress has been made in locoregionally advanced inoperable disease, mainly with the optimal combination of concurrent chemoradiotherapy and with the introduction of new active drugs, such as docetaxel, in the induction phase of the treatment. The association of docetaxel, cisplatin, and 5-fluorouracil (TPF) regimen is now acknowledged as being the gold standard of induction treatment. The subset of patients with recurrent/metastatic disease still carries a grim prognosis. For the time being, new biological therapies have not dramatically changed this scenario, even in combination with conventional treatments. Little is known about the role of docetaxel and, in general, of chemotherapy in the adjuvant setting, even though it is increasingly acknowledged that, beyond a certain risk, concurrent adjuvant chemoradiotherapy is required. The main aim of the research on head and neck cancer probably lies in the identification of biomolecular markers that are able to predict clinical behaviour, thus allowing appropriate treatment tailoring. The identification of human papilloma virus infection as the agent of a particular form of oropharyngeal cancer is an example of this strategy in consideration of the peculiar characteristics. *Anti-Cancer Drugs* 20:639–645 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is among the most common tumors worldwide, accounting for approximately 8% of total cancers [1]. Basically, three main settings in the presentation of head and neck cancer (HNC) can be acknowledged: namely, early-stage operable disease; locoregionally advanced inoperable disease; recurrent or metastatic disease. Operable patients can achieve cure in a wide proportion of cases, mainly with surgery, followed by radiotherapy or radiochemotherapy; however, these patients can have a favorable prognosis even without surgery, when organ preservation is the main endpoint. Patients presenting with locoregionally advanced inoperable disease, in contrast, have a poorer prognosis, only 30–50% of patients being alive up to 3 years [2]. Patients with recurrent or metastatic disease are deemed to have a grim prognosis in all cases, and chemotherapy is the only therapeutic option. The above consideration strengthens the need for new active drug discovery and for new treatment approaches to be used in the different settings of the disease.

Among the new cytotoxic compounds that have enriched the therapeutic armamentarium against SCCHN, docetaxel is probably the most inspiring one. In fact, preclinical data showed high docetaxel cytotoxicity against a variety of human cancer cell lines, particularly HNC [3]. Docetaxel was more effective than cisplatin in inhibiting the growth of two SCCHN xenograft models (HNX-14C and HNX-22B) [3]. These observations paved the way for a number of phase I/II clinical studies of docetaxel in different settings of SCCHN, administered either alone or in combination with other drugs or radiation therapy. Locally advanced inoperable disease is the main setting in which clinical studies with docetaxel have been carried out, and most of this study will focus on it.

Locally advanced inoperable disease

The treatment of patients with locally advanced inoperable SCCHN mainly includes the combination of concurrent chemotherapy and radiotherapy, which has now replaced radiotherapy alone. In fact, several randomized trials have shown that adding concurrent chemotherapy to radiation increased locoregional control by 15–20% in patients with locally advanced disease. Furthermore, an 8% increase in 5-year survival was reported in a recent meta-analysis [4–6] Cisplatin, administered at a dose of 100 mg/m^2 every 3 weeks for three cycles, concomitantly with radiation therapy, is the drug of choice in this setting. There are a number of theoretic advantages to the concomitant use of chemotherapy and radiation, including the fact that both treatments are independently active in this disease, allowing for the possibility that tumor cells resistant to one modality might still respond to the other [7]. Furthermore, systemic treatment, such as chemotherapy, is able to treat microscopic metastatic disease. However, concomitant

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chemoradiotherapy (CRT) is associated with severe acute toxicities, such as mucositis.

The role of induction chemotherapy is less clearly defined; however, there is some clinical evidence that it can provide a survival advantage [8–10]. The cisplatin–5-fluorouracil (5-FU) regimen (PF) was the best evaluated combination in this setting, and it has been chosen as the reference regimen in two large phase III studies of docetaxel, cisplatin, 5-FU (TPF) versus PF. In turn, selection of the TPF regimen for these studies was based on the results of earlier clinical trials [11,12] that showed more convincing activity and toxicity data of TPF, with respect to docetaxel–cisplatin combination. The first phase III study was carried out by the European Organization for Research and Treatment of Cancer [13]. Patients were randomized to receive four cycles of either TPF (both docetaxel and cisplatin at 75 mg/m^2 on day 1, 5-FU 750 mg/m^2 daily for 1–5 days, by continuous infusion) or standard PF (cisplatin 100 mg/m^2 on day 1, 5-FU 1000 mg/m^2 daily for 5 days). Radiotherapy was subsequently performed for 4–7 weeks after the end of chemotherapy with the use of either conventional fractionation, or accelerated or hyperfractionated regimen; neck dissection was considered for all patients before radiotherapy and 3 months after its completion. Progression-free survival was the main endpoint of the study and it was statistically different between the two treatment arms, with a clear advantage for TPF (11.0 vs. 8.2 months) ($P = 0.007$.) TPF induced a 27% reduction in the risk of death, with a median overall survival of 18.8 months versus 14.5 months in the PF arm. Overall response rates to chemotherapy were 68% in the TPF arm versus 54% in the PF arm ($P = 0.006$). The difference among complete response rates was not significant (9 vs. 7%, respectively). As for safety, TPF, as expected, was associated with more neutropenia, but not with more frequent infections when antibiotic prophylaxis was carried out. The toxic death rate was 2.3% in the TPF group and 5.5% in the PF group. Overall, the reduced doses of cisplatin and 5-FU were probably the determinants of the lower toxicity for the TPF regimen. Importantly, in this study, better efficacy and tolerability of TPF was accompanied by a significant treatment difference in quality of life ($P = 0.01$). In particular, speech and eating disturbances were greater in the PF arm [14]. The second phase III study was carried out by Posner *et al.* [15]. The treatment plan in this study was slightly different, as three cycles of induction TPF (docetaxel 75 mg/m^2 on day 1, cisplatin 100 mg/m^2 on day 1, and 5-FU 1000 mg/m^2/day for 4 days) were compared with three cycles of standard PF. Importantly, induction chemotherapy was not followed by radiotherapy alone, but by the combination of weekly carboplatin monotherapy (area under the concentration–time curve 1.5) and radiotherapy. Overall survival was the main endpoint of the study, with a minimum of 2 years of follow-up, and significantly more patients survived in the TPF group than in the PF group, median overall survival being 71 months and 30 months, respectively ($P = 0.006$). Locoregional control was better in the TPF group than in the PF group ($P = 0.04$), but the incidence of distant metastases did not differ significantly. The overall response rate after induction chemotherapy was 72% in the TPF arm (17% complete) and 64% in the PF arm (15% complete). None of these differences reached statistical significance. Although myelotoxicity was more frequent in the TPF group than in the PF group, treatment was more frequently delayed in the PF group [15]. Altogether, these two studies observe the increasing consideration that induction chemotherapy is gaining acceptance as standard treatment in the multidisciplinary management of locally advanced SCCHN. In particular, the three-drug combination of docetaxel, cisplatin, 5-FU can now be considered the reference regimen in this setting. The main results of the two studies are shown in Table 1. Which of the two variants of TPF has to be considered preferable? If we examine the survival data, the American version seems better, but the two studies are not easily comparable because of more dense TPF treatment, and the use of weekly carboplatin along with radiotherapy in the American study. Larynx preservation is an important endpoint in operable patients with hypopharingeal or laryngeal cancer, and during the 1990s, the benefits of PF induction chemotherapy were shown in two phase III trials, in which larynx preservation rate was

Table 1 Results of two phase III trials of TPF versus PF followed by radiotherapy or chemoradiotherapy

	Median PFS (month)	Median OS (month)	3-years PFS rate (%)	3-years PFS rate (%)	Antibiotic prophylaxis	GCSF prophylaxis	Response rate (%)
TAX 323							
TPF	11.0 HR: 0.72 (0.57–0.91)	18.8 HR: 0.73 (0.56–0.94)	17	37	Not allowed	Not allowed	68
PF	8.2	14.5	14	26	–	–	54
TAX 324							
TPF	36 HR: 0.71 (0.56–0.90)	71 HR: 0.70 (0.54–0.90)	49	62	Allowed on days 5–15	Not allowed	72
PF	13	30	37	48	–	–	59

GSCF, granulocyte colony-stimulating factor; HR, hazard ratio; OS, overall survival; PF, cisplatin 5-fluorouracil; PFS, progression free survival; TAX, docetaxel; TPF, docetaxel cisplatin 5-fluorouracil.

the main endpoint. Both of the studies compared radiation therapy preceded by either PF induction chemotherapy or standard surgery. Induction chemotherapy enabled larynx preservation in 64 and 42% of the patients in these two studies, respectively. Furthermore, fewer distant metastases occurred in the PF arm of both the studies. However, survival rates were similar in the two treatment arms [16,17]. The GORTEC 2000–2001 study investigated whether the addition of docetaxel to standard PF regimen would increase the larynx preservation rate. Patients were randomized to receive three cycles of TPF (European version) or PF, followed by either radiotherapy (if achieving an objective response) or total laryngectomy. The 3-year larynx preservation rate was the main endpoint and it was significantly higher in the TPF arm than in the PF arm (74 vs. 51%). In this study, TPF was also associated with a higher objective response rate (83 vs. 61%, $P = 0.0013$) with respect to PF [18].

Docetaxel integration in schemes of concomitant CRT is being investigated and promising results, with both TPF and docetaxel–cisplatin regimens, have been reported. Seiwert and co-workers [19] have developed a scheme of carboplatin–docetaxel induction chemotherapy followed by five cycles of concomitant docetaxel-based CRT. Thus, a phase I study ended up with a recommended dose of docetaxel of 25 mg/m^2 when assumed along with 5-FU, hydroxyurea, radiation (concomitant phase) and 35 mg/m^2 in combination with carboplatin induction [19].

TPF has already been tested as induction chemotherapy followed by concurrent CRT across a few phase II studies. In particular, TPF was followed by the same regimen coupled with radiation therapy in a Greek study [12], and by PF regimen plus radiation therapy in an Italian study [11]. In both trials, the combined treatment approach looked feasible and prompted two phase III trials of standard concomitant CRT versus docetaxel-based induction chemotherapy followed by concomitant CRT. A number of trials are ongoing in this setting [20] and some preliminary data seem to favor the sequential arm [21,22]. Other ways to improve the therapeutic index in locally advanced disease include the combination of either weekly [23,24] or biweekly [25] docetaxel plus radiation, whereas other ongoing trials are aimed at evaluating the contribution of concomitant boost fractionation to standard CRT [26]. Taken together, these initial studies show that, although moderately toxic (mucositis, skin toxicity), the combined treatment with docetaxel and radiation therapy is active at least with doses and schedules used up to now. In consideration of all the above findings [27], it is easy to foresee that in the near future the standard of care in patients with locally advanced inoperable disease will change.

Recurrent/metastatic disease

For patients with recurrent or metastatic disease, chemotherapy represents the mainstay of treatment. However, response rates are approximately 30% and response duration does not exceed 6–8 months, with a median overall survival of 6–9 months [28,29]. Docetaxel has been widely used in patients with recurrent/metastatic SSCHN, both alone and in combination with other drugs or radiation therapy. Three phase II studies with single-agent docetaxel produced response rates ranging between 21 and 42% [30–32]. More recently, Hitt *et al.* [33] have published a phase II study of docetaxel in 38 patients with recurrent/metastatic SCCHN. A weekly schedule of docetaxel 30 mg/m^2 for 4 out of 5 weeks was used in this study. The drug showed substantial activity with responses observed in 42% of patients, median duration of 8.39 months, estimated median survival of 11.3 months, and a 1-year survival rate of 39%. Toxicity was acceptable, as no grade 3–4 toxicity was observed and no treatment delays or dose reductions were required. A randomized phase II study comparing docetaxel and methotrexate was carried out in patients with recurrent HNC. This study confirmed the activity of the drug, as the response rate was 27% (95% confidence interval 21.7–32.3%) in the docetaxel arm versus 15% (95% confidence interval 11.2–18.8%) in the methotrexate arm. However, overall survival and time to progression were superimposable between the two treatments [34]. There is evidence that docetaxel is also active in second-line treatment of recurrent disease; a 10% overall response rate and a 25% tumor control rate in platinum refractory metastatic or recurrent HNC was reported in a Japanese study [35]. Docetaxel has also been studied in combination with cisplatin in several clinical trials. Phase I/II studies of docetaxel and cisplatin every 3 weeks were carried out both in recurrent/metastatic disease and in locally advanced disease as induction therapy before radiotherapy [36–42]. Severe myelotoxicity represented the main concern across all these studies. In our study [42], toxicity was particularly heavy, probably because of the higher cisplatin dose (100 mg/m^2), and two patients died of febrile neutropenia complicated by sepsis. The weekly schedule has been less frequently used, but it seems to have a more favorable toxicity profile [40]. Baghi *et al.* [43] have evaluated TPF activity in recurrent SCCHN. This study, although small, showed interesting results in terms of response rate, median recurrence-free survival, and median survival.

Combination studies of docetaxel or docetaxel-based regimens and radiation therapy have also been carried out in recurrent disease. In general, these studies have turned out to be positive, highlighting that radiosensitizing properties of docetaxel are generally able to increase the activity of radiotherapy, mainly with the hyperfractionated schedule [23–25]. Finally, it is worth mentioning that new taxanes are being studied in HNC.

Ixabepilone is a new epothilone that has been tested in two different schedules by the Eastern Cooperative Oncology Group. The drug was active in taxane-naive patients, but its severe neurotoxicity prevented it from being further developed in HNC [44].

Adjuvant setting

SCCHN patients with early-stage disease can be successfully treated with a locoregional approach, generally including surgery, followed by radio or radiochemotherapy. Radiation therapy, administered either with conventional fractionation or with different schedules, is considered mandatory in the presence of involved nodes. When the patient is considered high risk because of the presence of either close resection margin (< 0.5 mm) or extracapsular invasion of at least one involved node, a combined CRT approach is indicated. The potential benefit of adding chemotherapy to postoperative radiation has been tested in a few randomized clinical trials [45–47]. The ideal way of combining the two treatment modalities in this setting is to give radiation therapy according to conventional fractionation and concomitant cisplatin at the dose of 100 mg/m^2 on days 1, 22, and 43. In several patients, larynx preservation techniques, with concurrent and sequential CRT, may be a major focus, as they allow the patient to preserve voice, speech, and ability to swallow. In these cases, even at early stages, surgery has to be avoided, and radiation therapy may represent the mainstay of treatment.

Is there any role for docetaxel in the adjuvant setting? A small study was recently carried out in 20 patients and showed that TPF regimen was safe and effective when given in the adjuvant setting in patients who had undergone surgery of the primary tumors and regional lymphnodes. In fact, the safety profile was acceptable; mucositis (two patients) and febrile neutropenia (four patients) represent the main toxicities. After a median follow-up of 16.5 months, median time to progression was 20 months, and the estimated overall survival at the median time of follow-up was 90% [48].

Biological therapies: the future?

A further field of development in systemic treatment for advanced disease includes the combined treatment of chemotherapy and biological agents. More in general, TPF could be considered the new platform to which new (biological) agents should be added. As a result of the high epidermal growth factor receptor (EGFR) expression in SCCHN [49] and the adverse prognostic significance it carries [49], EGFR-targeted drugs have been widely used in HNC, both alone and in combination. Cetuximab, a chimeric monoclonal antibody anti-EGFR, is now a reference drug in locally advanced inoperable SCCHN in combination with radiotherapy [50] and in recurrent/metastatic disease in combination with cisplatin and 5-FU [51]. The addition of cetuximab to TPF regimen in the induction setting is being actively pursued [52,53]. Fury *et al.* [54], based on their xenograft model, showed that intermittent high-dose gefitinib was able to sensitize tumors to subsequent treatment with taxanes, carried out a phase I trial to explore docetaxel in combination with escalating doses of intermittent gefitinib given before docetaxel. High-dose gefitinib given for 2 days before docetaxel seemed feasible in patients with advanced solid tumors. A patient with advanced HNC had a partial response. Neutropenia qualified as dose-limiting toxicity and the recommended dose for phase II was 2250 mg of gefitinib orally on days 1 and 2 followed by 75 mg/m^2 of docetaxel intravenously on day 3 of a 21-day cycle. The enhancement of docetaxel-induced cytotoxicity by blocking EGFR in HNC has also been shown by Choe *et al.* [55], and this lends further support to the ongoing phase III study evaluating docetaxel with or without gefitinib in patients with recurrent or metastatic HNC. Erlotinib was investigated in combination with docetaxel and cisplatin in patients with recurrent or metastatic SCCHN never pretreated with chemotherapy. Among 43 patients, a 67% overall response rate was reported, with a median progression-free survival of 6 months and a median survival of 11 months [56]. Panitumumab, a fully human monoclonal antibody anti-EGFR, is also being tested in a two-arm phase II trial evaluating docetaxel and cisplatin combination with or without panitumumab as first-line treatment for patients with recurrent or metastatic disease [57]. Tumor-signalling pathway components that work in cooperation with EGFR or provide compensation for the loss of EGFR-initiated signaling are suitable targets for therapies administered either alone or in combination with EGFR-targeted agents. Src-targeted compounds, such as dasatinib and AZD-0530, which are both dual Src/Abl inhibitors, are undergoing clinical studies [57]. Finally, studies are in progress with bortezomib, a proteasome inhibitor, which has been shown to increase the cytotoxic activity of docetaxel and cisplatin in HNC cell lines [57]. In-vivo and in the clinical setting, the addition of bortezomib may allow the reduction of the doses of both docetaxel and cisplatin, thus substantially lowering their toxicity [58].

Conclusion

HNC is a group of tumors whose incidence is rising, and whose prognosis remains grim in the majority of cases. However, evidence is mounting that SCCHN represents a fairly heterogeneous group of diseases whose biomolecular characteristics may differ, thus providing the basis for tailored treatments [7].

For example, recent evidences have accumulated pointing to human papilloma virus type-16 and 18 as the etiologic agents of a particular form of advanced oropharyngeal carcinoma, the epidemiologic, clinical, and prognostic features of which differ from the most

common HNC types. In fact, this type of tumor mainly occurs in younger people who do not smoke or drink, and it has a less aggressive clinical behavior and a more favorable prognosis. It may need a different treatment approach, and, in future trials in HNC, it might be considered a stratification factor [59].

A number of issues are crucial in dealing with the treatment of SCCHN. The important phase III study carried out by Posner *et al.* [15] assumed that weekly low-dose carboplatin in association with radiotherapy is validated enough as concurrent CRT. Phase III data are awaited to properly address this controversial issue.

Medical oncologists and, probably first, head and neck oncologists, in the recent past have greatly relied on the introduction of biological drugs, with the aim of improving the therapeutic index. However, clinical data have only partly matched expectations. As cetuximab has gained a definite role in the therapeutic armamentarium of HNC [50,51], much less convincing data have been reported with EGFR tyrosine kinase inhibitors, either alone [60] or in combination with radiotherapy [61]. The discovery of new crucial targets and, consequently, of new specific biological drugs, is still among the greatest challenges in medical oncology. It is now increasingly acknowledged that biological drugs are suitable for use in combination with chemotherapy, sometimes with different doses and schedules. In fact, preclinical data have shown that daily gefitinib at conventional doses suboptimally inhibits EGFR phosphorylation and downstream survival pathways in tumors with wild-type EGFR. In contrast, intermittent high-dose gefitinib has been shown to overcome these problems, and this has led to a phase I trial of intermittent high-dose gefitinib and fixed-dose docetaxel in patients with advanced solid tumors [54].

The toxicity of the treatment, in particular, in patients who undergo concurrent CRT, is another major problem that oncologists have to cope with. In particular, as median survival is increasing, problems inherent in late toxicities are being observed with increasing frequence. Late xerostomia is among the most disturbing side effects, and both medical (amifostine) and radiotherapic (intensity-modulated radiation therapy) approaches have been used to overcome it [7]. Mucositis is known to be the most typical and disturbing side effect, and it occurs both at early and at late stages during CRT. A great deal of effort has been made to tackle this side effect, mainly with the development of palifernim, a human keratinocyte growth factor, which, upon binding to its receptor, results in proliferation, differentiation, and migration of epithelial cells [59].

In conclusion, we can state that the overall outcome of patients with advanced SCCHN (especially those affected by locally advanced inoperable disease) is improving, in part also because of the introduction of docetaxel in the front-line induction regimen. However, the real role of induction chemotherapy will be clarified by ongoing phase III trials [22]. The global treatment strategy is not devoid of toxicity, and wide room for improvement exists. In particular, the results of combination of cetuximab with TPF in the induction setting are examined with interest. The final step will consist in appropriately identifying biomolecular markers that can exactly unravel the prognosis, thus driving the clinician appropriately in his treatment decisions.

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