

Concurrent Chemo-radiotherapy with Taxotere and Cisplatin in Head and Neck Cancer: A Feasibility Study

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Abstract. *Background:* For many years surgery was the cornerstone of treatment for head and neck cancers and radiotherapy was the treatment of choice in adjuvant and advanced inoperable settings. Recently, induction sequential chemotherapy followed by radiotherapy has shown good tolerability and has prolonged the median overall survival. *This phase II trial explored the feasibility of the concurrent association with radiotherapy of a full-dose chemotherapy based on an original schedule of docetaxel and cisplatin. Patients and Methods:* Twenty-four patients with head and neck squamous cell carcinoma (HNSCC) were enrolled. Taxotere (docetaxel) was administered on day 1, weekly for 6 weeks. The dose was 33 mg/m² /w. Cisplatin was administered on day 2 at the dose of 70 mg/m². Radiotherapy delivered was 60 Gy divided in 30 administrations over 6 weeks. *Results and Conclusion:* This schedule of treatment for HNSCC proved feasible. Appropriate support treatment, however, appears to be necessary for the feasibility of this concurrent chemo-radiotherapy.

Head and neck squamous cell carcinoma (HNSCC) is the most common malignant neoplasm of the mucosa of the upper aerodigestive tract. Nearly two-thirds of HNSCC patients present with advanced (Stage III or IV) disease and fifty per cent die of their disease (1). Accordingly, currently available therapeutic modalities (surgery, radiation and/or chemotherapy) need to be combined to achieve better survival results.

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For many years surgery was the cornerstone of treatment, while radiotherapy was the strategy of choice for head and neck cancer in adjuvant and advanced inoperable settings.

In recent years, however, induction sequential chemotherapy with platinum compounds plus 5-FU followed by radiotherapy, usually hyperfractionated radiotherapy, has shown good tolerability and has yielded more satisfactory clinical benefit than radiotherapy alone (2-4). Moreover, concomitant radio-chemotherapy with platinum analogs significantly prolongs the 3-year survival and median overall survival (OS) (5-7).

New drugs are now entering the therapeutic arena, gemcitabine and taxanes being the most promising compounds. Little is known, however, about how to associate these drugs with radiotherapy; moreover, toxicity assessment of the new protocols is essential, especially in an adjuvant setting.

Docetaxel is one of the most promising new drugs against HNSCC. One phase I study (8) evaluated the activity and tolerability of concurrent docetaxel and cisplatin radiosensitization with hyperfractionated irradiation in advanced disease. Both drugs were administered at radiomimetic dosages. The maximum tolerated doses were 13 mg/m²/w for docetaxel and 10 mg/m²/w for cisplatin. One phase I study (9) explored the association of docetaxel alone and radiation, recommending a dose of 15 mg/m²/w; this dose had little systemic effect.

A phase II study (10) administered 20 mg/m²/w of docetaxel in association with radiation therapy.

Several phase II studies have associated docetaxel alone or with carboplatin and/or 5-FU to radiotherapy in advanced or neoadjuvant settings (11, 12, 14, 15); the optimal association is still controversial, however. Disease-free survival and locoregional control are matters of concern, as are distant metastases. Full-dose chemotherapy should, nevertheless, afford better results.

This phase II multicentric non-randomized trial explored the feasibility of the association with radiotherapy of full-dose

chemotherapy based on an original schedule of docetaxel and cisplatin. The primary end-point of this study was the feasibility of treatment, with toxicity assessment being the secondary end-point.

Patients and Methods

Treatment is feasible if at least 70% (P1) of patients complete treatment. Treatment is not feasible if fewer than 40% (P0) of patients end it. According to Fleming's one step design, with a power of 80% and a mistake of I type rate of 5%, 24 patients must be enrolled, with at least 17 ending therapy, for treatment to be considered feasible.

We treated 24 consecutive chemotherapy- and radiotherapy-naive patients with concomitant radiotherapy (6000 cGy in 6 weeks) and chemotherapy.

High energy radiotherapy was performed. Treatment was planned with TPS. 0.5-1 cm CT images were used to define the target volume and sensitive non-target structures. The total dose delivered was 50 Gy, divided into 25 administrations over 5 weeks. A boost of 10 Gy divided into 5 doses was administered to bulky disease or to the surgical field. The spinal cord was excluded at the dose of 50 Gy.

Taxotere was administered on day 1, weekly for 6 weeks. The dose was 33 mg/m² /w. Cisplatin was administered on day 2 at the dose of 70 mg/m². The treatment schedule is reported in Table I.

The median age of the patients was 57 (47-70) years. Performance status was always <2 (0-1). Squamous cell carcinoma was the histotype for all patients. Ten patients had locally advanced inoperable or metastatic cancer. Fourteen patients were in an adjuvant setting. The inclusion criteria are listed in Table II, while Table III reports patient profiles.

The protocol design allowed for 1 week of suspension of any treatment in case of any grade 4 toxicity and the use of antiemetics and of G-CSF and Erythropoietin alfa (Ortho-Biotech) at doses and scheduling according to ASH-ASCO guidelines. Patients in whom grade 4 toxicity persisted for 2 weeks were dropped from the protocol and were evaluated negatively for feasibility. Enteric and parenteral nutritional support were permitted. Toxicities were assessed according to NCI-CTC guidelines.

All patients gave their informed consent; the study was cleared by the Ethics Committee of our institution, and was performed in accordance with the Declaration of Helsinki (1975).

Results

All patients ended the treatment. However, several toxicities of concern were recorded: mucositis was present in 22 patients, of whom 8 patients were grade 1, 8 were grade 2, 3 were grade 3 and 3 were grade 4. The worst mucositis was observed in all patients during the fifth week of treatment. All patients with grade 3-4 mucositis required parenteral nutritional support in a day hospital setting. In all patients with grade 4 mucositis drug administration and radiotherapy were delayed for 1 week. One patient with grade 4 mucositis required short inward treatment because of contemporary grade 3 febrile neutropenia and grade 2 anemia.

Table I. *Treatment schedule.*

Drugs or radiotherapy	Days
Taxotere 33 mg/m ²	Days 1,8,15,22,29,35
Cisplatin 70 mg/m ²	Day 2
Radiotherapy 50 Gy + 10 Gy boost	Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40

Table II. *Inclusion criteria.*

- 1) Age 18-75
- 2) Histologically proven squamous cell carcinoma of the head and neck
- 3) Written informed consent
- 4) PS 0-1(ECOG)
- 5) Hb >10 g/dl; PLT >100,000; WBC > 4000
- 6) Normal renal function
- 7) Liver tests up to 2 times/ normal values

Table III. *Patient profile.*

Median age	57 (47-70)
Male/female	18/6
PS	0 for 15 pts, 1 for 9 pts
Adjuvant/advanced	14/10

Neutropenia was recorded in 8 patients: 1 patient was grade 1, 2 patients were grade 2 and 5 patients were grade 3. All patients but 1, who developed febrile neutropenia, were asymptomatic.

Anemia of grade 2 developed in only 1 patient. Peripheral neuropathy of grade 1 developed in 3 patients. The toxicities are listed in Table IV.

Discussion

Several randomized studies and meta-analyses (16, 17) have shown that, compared with conventional radiotherapy, simultaneous radio-chemotherapy prolongs survival in patients with unresectable HNSCC. Moreover, the preservation of pharyngeal and laryngeal function and structure has dominated the development of newer treatment approaches. This prospective phase II trial was conducted to evaluate the feasibility and the toxicity of weekly docetaxel associated with cisplatin.

These two drugs were chosen because cisplatin is the gold standard drug in HNSCC and docetaxel has satisfactory single agent activity. Moreover, docetaxel was recently combined with several drugs (5-FU, Irinotecan) (18-20) and showed a good tolerability profile. It has also been combined with other less used drugs such as celecoxib and erlotinib (21,

Tables IV. *Toxicities.*

Toxicities-grade	No. of patients
Mucositis grade 1	8
Mucositis grade 2	8
Mucositis grade 3	3
Mucositis grade 4	3
Neutropenia grade 1	1
Neutropenia grade 2	2
Neutropenia grade 3	5
Neutropenia grade 4	0
Anemia grade 1	1
Anemia grade 2	0
Anemia grade 3	0
Anemia grade 4	0
Peripheral neuropathy grade 1	3
Peripheral neuropathy grade 2	0
Peripheral neuropathy grade 3	0
Peripheral neuropathy grade 4	0

22). In fact, interrupting the epidermal growth factor receptor signaling pathway has shown promise in a variety of cancers, and preclinical data has demonstrated possible synergies with platinum and taxanes. Because these new targeted drugs will be increasingly used in the future, it is very important to define schedules of classic drug combinations and their optimal synergy with radiotherapy. The schedule of treatment presented here for HNSCC appears feasible.

In our study, toxicity was severe, but not to the extent that it required the exclusion of patients. An appropriate support treatment, nonetheless, appears to be necessary for the feasibility of the applied concurrent chemo-radiotherapy. However, this support treatment was given in only 25% of patients, which is not very different from what is usually given to patients receiving classic alternate or sequential schedules.

Further studies are required to assess the efficacy of this treatment in both adjuvant and advanced settings. Associations with new targeted drugs (such as Erlotinib) may be explored, too, in order to improve treatments and the survival of patients affected by head and neck cancer.

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