Abstract

Introduction Concurrent chemotherapy and radiotherapy is recommended for the treatment of locally advanced unresectable head and neck (H&N) cancer.

Objective The primary purpose of the Phase I part of the study was to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT) and recommended dose (RD) of docetaxel with hyperfractionation radiotherapy. The primary objective of the Phase II part was to determine the response rate to the RD of treatment and, secondarily, to assess the toxicity of the schedule, time to progression, duration of response and overall survival (OS).

Materials and methods Patients (n=9 in Phase I; n=19 in Phase II) had unresectable H&N cancer. The starting docetaxel dose was 20 mg/m² plus hyperfractionated radiotherapy. Ramping of docetaxel was 5 mg/m² if MTD was not reached.

Results MTD of docetaxel was 20 mg/m². Limiting toxicities were grade 4 pneumonia and grade 4 mucositis. The RD was 15 mg/m². Phase II initial response was 76% (CR=18%; PR=9%); updated response was 89% (CR=59%; PR=29%). The median progression-free survival was 7.8 months (95%CI: 0–22.3) and the median OS was 15.1 months (95%CI: 0–35.9). Grade 3–4 toxicities included mucositis (91%), pneumonia (27%) and fatigue (27%). There were 5 toxic deaths (2 from intestinal perforation, 3 from pneumonia).

Conclusions Weekly docetaxel+hyperfractionation radiotherapy is active but with high toxicity rates and, hence, this treatment regimen would be difficult to justify.

Keywords Hyperfractionation radiotherapy · Docetaxel · Phase I · Phase II · Head and neck cancer

Introduction

About 60% of patients with head and neck (H&N) squamous cell carcinoma have locally advanced disease at diagnosis. Surgery, radiation therapy or both have been used to achieve locoregional control, but with poor results [1]. Concurrent therapy with platinum-based chemotherapy and radiotherapy is an accepted standard for definitive treatment of locally advanced H&N carcinomas [1–3]. New radiotherapy schedules have been designed to increase the dose intensity. However, these regimens are associated with increased toxicity, mostly mucositis and fibrosis [4, 5].

Recently, results from a meta-analysis analysing the effect of altered fractionation radiation therapy in overall survival (OS) of patients with H&N carcinoma showed an absolute benefit of 3.4% at 5 years vs. conventional radiotherapy (p=0.003). The benefit was significantly higher with hyperfractionation radiotherapy (8% at 5 years). There was also an improvement in locoregional control in favour of altered fractionation (6.4% at 5 years, p<0.0001) [3, 4].

Therapies that included taxanes have also been investigated in H&N carcinoma. In the neoadjuvant and palliative setting the toxicity profiles are favourable and the response is improved [6–8]. Docetaxel is a semisynthetic agent that enhances tubulin polymerisation and inhibits microtubule depolymerisation [9], with a radiosensitising capability that has been demonstrated in vitro [10].

In lieu of any published experience with docetaxel and hyperfractionation radiotherapy, this Phase I/II study was designed to assess the efficacy, in terms of toxicity and response rate, of this combination. However, some trials
assessing the role of docetaxel and radiotherapy for the treatment of locally advanced H&N carcinoma have been published since we conducted this trial [7, 10–15].

The primary purpose of our study was to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT) and the recommended dose (RD) of weekly docetaxel in combination with hyperfractionation radiotherapy in locally advanced H&N cancer (Phase I study). In the Phase II part of the study, the primary purpose was to determine the response rate of patients to the weekly RD identified in the Phase I study. The secondary purposes were to evaluate toxicity of the schedule and to obtain additional efficacy data such as time to progression (TTP), duration of response and OS.

Patients and methods

Patients

Patients eligible for this study were required to have histologically proven locally advanced squamous cell carcinoma of the oral cavity, oropharynx, larynx or hypopharynx. Cancers of the nasopharynx, nasal cavity and paranasal sinus sites were excluded. The tumour needed to be considered as unresectable by a multidisciplinary team that included members of the medical oncology, radiation oncology and H&N surgery teams. Tumours needed to have at least one measurable lesion.

Inclusion criteria were as follows: signed written informed consent; age 18–75 years; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; expected survival >3 months; adequate haematological function (neutrophil count ≥2.0×10⁹/l, platelet count ≥100×10⁹/l, haemoglobin ≥10 g/l); adequate hepatobiliary function (serum aspartate aminotransferase and alanine aminotransferase ≤2.5 the upper limit of the normal range (ULN), serum bilirubin ≤1×ULN, alkaline phosphatase ≤5×ULN); adequate renal function (creatinine ≤1.25 mg/dl or 120 µmol/l, or calculated clearance ≥60 ml/min); and adequate nutritional status (weight loss <20%, albumin ≥35 g/l). No previous chemotherapy or radiotherapy for the disease was permitted in the study protocol. Patients should not have been prescribed corticosteroids in the previous 6 months except if prescribed at low doses (≤20 mg prednisone or equivalent). The trial was approved by the local ethics committee of each participating institution.

Treatment and dose escalation schedule

Phase I study: determination of MTD and RD

The Phase I study was designed to determine the RD of docetaxel in combination with hyperfractionation radiotherapy. Docetaxel dose escalation was scheduled for the Phase I study starting from level 1. Six patients were enrolled in each dose level. Step-up to the next dose level was performed when two or fewer patients had DLT during the chemoradiotherapy or 4 weeks after the end of the treatment. When three or more patients showed DLT the dose of that level was considered the MTD. The Phase II part of the study was conducted with the RD as determined in the Phase I study, i.e., one step below the MTD. If MTD was reached in level 1, level −1 was then explored. At least three patients needed to have received the complete treatment and had to have been monitored over 3 weeks between the first patient and the rest of the patients at the same dose level. Intra-patient escalation and dose reduction were not allowed within the protocol. When the RD level was defined, the study continued as for the Phase II study. Patient substitution due to major protocol violation was permitted.

Docetaxel was administered weekly as a 30-min intravenous infusion. The first dose was administered on the last working day before the start of the radiation therapy and was repeated weekly, in the afternoon if possible (usually on a Friday in order to have a 48–72 h interval before commencing the radiotherapy on the Monday) [16]. The last dose of docetaxel was administered the week before the end of radiation therapy. Anti-emetic treatment was administered according to local practice. To reduce hypersensitivity reaction as well as cutaneous toxicity and oedema, dexamethasone (8 mg oral) or equivalent corticosteroids were administered 12 h and 1 h prior to the docetaxel infusion, and 12 h post-infusion.

The starting dose level of docetaxel was 20 mg/m². Escalations of 5 mg/m² were scheduled for the next dose level if MTD was not reached. Dose reduction was not allowed within the protocol. In case of toxicity ≥grade 2, docetaxel infusion was interrupted until the toxicity was reduced to <grade 2 within a maximum period of 2 weeks. Docetaxel treatment was discontinued if any grade 3 non-haematological toxicity was observed. Protocol recommendation was to maintain haemoglobin >10 g/l and blood transfusion was indicated for patients with a decrease in haemoglobin below this level. Erythropoietic agents were not permitted within the protocol.

Acute toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria version 1.0 (NCI-CTC) and late toxicity was evaluated according to EORTC/RTOG Criteria [17, 18]. DLT was defined as follows: (1) grade 4 neutropenia ≥5 days or associated with fever ≥38°C or ≥grade 3 infection; (2) febrile neutropenia (fever ≥38.1°C with grade 3 or 4 neutropenia); (3) sepsis with grade 3–4 neutropenia; (4) grade 4 thrombocytopenia; (5) symptomatic thrombocytopenia (bleeding); (6) grade 4 mucositis causing a suspension of the radiotherapy >2 weeks; (7) grade 4 mucositis occurring within the first 4 weeks of chemoradiotherapy; (8) grade 3–4 mucositis associated with grade 3 fatigue (with deterioration of performance status ≥2, or a decrease of 40% in the Karnofsky