Docetaxel versus Docetaxel and Lapatinib in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). An open label multicenter randomized phase II study.
A study of the Dutch Head and Neck Cancer Group (DHNCG) (NWHHT 08-02).

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22962

Source
NTR

Brief title
TyvTax study

Health condition

patients with recurrent SCCHN not amendable for local therapy or patients with metastatic SCCHN
Keywords: SCCHN, recurrent and/or metastatic disease, docetaxel, lapatinib

Sponsors and support

Primary sponsor: The Netherlands Cancer Institute Antoni van Leeuwenhoek hospital

Dutch Head and Neck Cancer Group (DHNCG)
Source(s) of monetary or material Support: Glaxo Smith Kline & Sanofi Aventis

Intervention

Outcome measures

Primary outcome

The aim of this study is to select the candidate treatment with the highest level of activity for subsequent phase III testing (selection design). Activity is defined as clinical benefit (CR, PR or stable disease) in patients with recurrent SCCHN not amendable for local therapy or metastatic SCCHN. Clinical benefit will be assessed in week 8, i.e. after two courses of docetaxel.

Secondary outcome

1. To evaluate the two treatment groups with respect to the following: Progression free survival (PFS), overall survival (OS) and efficacy (defined as CR + PR);

2. To determine the qualitative and quantitative toxicities associated with docetaxel and lapatinib or docetaxel only in subjects with local or locoregional recurrence not amendable for local therapy or metastatic disease;

3. To evaluate volumetric tumour responses and to correlate those with tumour responses based on RECIST criteria;

4. To evaluate and compare quality of live in the two treatment groups using Quality of life questionnaire (QLQ)-C30 (Version 3.0) and the head and neck cancer-specific QLQ-H&N35.

Study description

Background summary

Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of newly diagnosed cancers in adult patients. Worldwide more than 500.000 new cases are diagnosed annually. It is a potentially curable malignancy when diagnosed at an early stage. Unfortunately, 60% of the patients present with advanced irresectable locoregional disease. In this group of patients the prognosis is quite poor. Only 30% to 50% will be alive after 3 years following standard therapy.(1) Sixty to 70% will develop locoregional recurrences within 2 years and 30% will develop distant metastases. Prognostic factors that have been predictors of durable response include T and N stage, tumor differentiation, primary tumor site, performance status and genetic markers such as mutation of p-53 oncogenes. Patients with recurrent

and/or metastatic SCCHN have a dismal prognosis with a medium survival time around 5-9 months and a poor quality of life. Depending on previous treatment, site of relapse, performance status and co-morbidities several therapeutic interventions are advocated, i.e. salvage surgery, re-irradiation, photodynamic therapy, palliative chemotherapy and best supportive care. Although these palliative treatments resulted in a temporarily amelioration of symptoms no increase in survival was observed over the past twenty-five years. In the Netherlands according to the national treatment guidelines treatment with methotrexate (with a RR 15%) is often advocated in patients with recurrent and/or metastatic SCCHN.The epidermal growth factor receptor (EGFR) plays a pivotal role in the development and survival of epithelial tissues. Almost all SCCHN express EGFR and the expression of EGFR and one its ligands TGFβ has been linked to poor outcome in patients undergoing therapy.(2;3) In addition modulation of EGFR signaling in preclinical models of SCCHN by either small molecules or monoclonal antibodies has demonstrated remarkable activity.(4-8) In clinical trials in patients with recurrent and/or metastatic SCCHN small-molecule tyrosine kinase inhibitors with activity against EGFR have demonstrated an overall response rate of approximately 10-15%.(9-11) Clinical trials with cetuximab, a monoclonal antibody raised against the extracellular domain of EGFR, have demonstrated a overall response rate of 11-13% and a disease control rate of 51% in patients with platinum resistant recurrent and/or metastatic SCCHN.(12;13) Preclinical models have also demonstrated both for small molecules and monoclonal antibodies against EGFR that application of these drugs can overcome or reduce the tumor resistance against chemotherapy or radiotherapy.Bonner et al. have performed a landmark study in the clinical use of EGFR inhibitors in patients with locally advanced SCCHN. Addition of cetuximab to radiotherapy (n=211) resulted in a median overall survival of 49.0 months compared to 29.3 months among patients treated with radiotherapy alone (HR 0.74, p=00.3).

To date, based on three meta-analyses, first-line therapy in locally advanced SCCHN consists of concomitant chemotherapy and radiotherapy, which results in a absolute benefit in survival at 2 and 5 years of 8 % in comparison with radiotherapy alone. In addition, after promising results, i.e. 3-yr OS rate of 76% with concurrent chemoradiation and cetuximab in a phase II study by Pfister et al. in patients with locally advanced SCCHN, several large randomized phase III trials are on going to investigate if addition of cetuximab to concurrent chemoradiation will improve the efficacy in first line treatment of locally advanced SCCHN. Recently, Vermorken et al. have demonstrated that addition of cetuximab to platinum based chemotherapy resulted in a prolongation of the median overall survival from 7.4 months to 10.1 months (HR 0.8, p=0.04) in patients with recurrent and/or metastatic SCCHN. This study has demonstrated prolongation of the overall survival in this patient group for the first time in twenty five years. This observation emphasizes that modulation of EGFR in combination with chemotherapy could be a valuable treatment modality in patients with recurrent and/or metastatic SCCHN.Thus, combination of doxetaxel and lapatinib in treatment of recurrent and/or metastatic SCCHN may result in better outcome and may reduce treatment related toxicity.

Study objective

To date first line therapy in locoregionally advanced SCCHN consist of concurrent chemotherapy, i.e. cisplatin 100 mg/m² i.v d1,22,43, and radiotherapy. Therefore in recurrent

and/or metastatic SCCHN treatment with cisplatin containing regimens might not be most advantageous. Furthermore cisplatin containing regimens cannot be administered in an outpatient clinic approach and result in considerable toxicity, i.e. renal impairment, peripheral neuropathy and ototoxicity.

In preclinical studies enhancement of docetaxel induced cytotoxity was observed in six human cell lines of SCCHN by gefitinib, a small-molecule tyrosine kinase inhibitor with activity against EGFR, and celecoxib, a cyclooxygenase-2 inhibitor.Thus, combination of doxetaxel and lapatinib in treatment of recurrent and/or metastatic SCCHN may result in better outcome and may reduce treatment related toxicity. Recently, LoRusso et al. have performed a phase I study of lapatinib (1250 mg O.D.) and docetaxel 75 mg/m2 (once every 3 weeks) in 52 patients with advanced solid tumors. Adverse events were mild to moderate in severity and consisted primarily of diarrhea, rash, fatigue and nausea. Dose limiting toxicity consisted of neutropenia. There were no interactions in pharmacokinetics between lapatinib and docetaxel, i.e. lapatinib: mean AUC , Cmax and Tmax were 14.2 (24h), h.mg/ml, 1.29 mg/L, 3.00 h, respectively, docetaxel, i.e. AUC (to infinity), clearance and steady-state volume of distribution 2.47 h.mg/ml, 30.4 L/h/m2, 114 L/m2, respectively. Therefore a phase II study using the same dosing scheme - lapatinib 1250 mg O.D. and docetaxel 75 mg/m2 (once every 3 weeks) – is indicated.

The aim of this study is to select the candidate treatment with the highest level of activity for subsequent phase III testing. Activity is defined as clinical benefit (CR,PR or stable disease) in patients with recurrent SCCHN not amendable for local therapy or metastatic SCCHN. Clinical benefit will be assessed in week 8, i.e. after two courses of docetaxel.

To evaluate the two treatment groups with respect to the following: progression free survival (PFS), overall survival (OS), efficacy (defined as CR + PR).

Secondairy endpoints:

To determine the qualitative and quantitative toxicities associated with docetaxel and lapatinib or docetaxel in subjects with local or locoregional recurrence not amendable for local therapy or metastatic disease.

To evaluate volumetric tumor responses and to correlate those with tumor responses based on RECIST criteria.

To evaluate and compare quality of live in the two treatment groups using Quality of life questionnaire (QLQ)-C30 (Version 3.0)and the head and neck cancer-specific QLQ-H&N35.

Study design

Patients will be followed by CT-scan at baseline, after every 2nd cycle of docetaxel until disease progression or discontinuation of the study. QLQ and if necessary EMT evaluation will take place at the same time points as the CT-scans After disease progression or study withdrawal follow up will continue every 3 months for the first 2 years and every 6 months thereafter until death.

Intervention

Patients will be randomised between two study arms, i.e:
1. Arm A: Docetaxel at a dose of 75 mg/m² as 1 hour i.v. infusion on day 1 every 3 weeks until disease progression;

2. Arm B: Docetaxel at a dose of 75 mg/m² as 1 hour i.v. infusion on day 1 every 3 weeks and Lapatinib 1250 mg o.d. day 1 and every day thereafter continuously until disease progression.

Prophylactic G-CSF therapy:

All patients must receive prophylactic pegfilgrastim (Neulasta®) in order to prevent docetaxel related neutropenia and/or its complications (fever and infection). These injections have a fixed dose of 6 mg and can be given once per chemotherapy cycle on day 2, independent of body weight and should be given 1 day after the chemotherapy administration.

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Eligibility criteria

Inclusion criteria

1. ≥18 years of age;

2. Histologically or cytologically confirmed diagnosis of SCCHN;

3. Local or locoregional recurrence not amendable for local therapy or metastatic disease;

4. Tumor tissue available for immunohistochemical evaluation of EGFR 1 and 2 expression;

5. WHO performance 0-2;

6. Measurable or evaluable disease (RECIST);

7. Effective contraception for both male and female subjects if risk of conception exists;

8. Neutrophils ≥1.5 x 109 cells/L, platelet count ≥ 100 x 109 cells/L and hemoglobin ≥ 6 mmol/L;

9. Total bilirubin within normal institutional limits (ULN);

10. Aspartate-aminotransferase (AST) and alanine-aminotransferase (ALT) ≤2,5 × ULN;

11. Creatinine clearance > 60 mL/min;

12. Cardiac ejection fraction ≥ 50% as measured by echocardiogram or MUGA scan;

13. Signed written informed consent before any study related activities are carried out;

14. Expected adequacy of follow-up.

Exclusion criteria

1. Patients previously treated with EGFR inhibitor;

2. Patients previously treated with Docetaxel or Paclitaxel;

3. Nasopharyngeal carcinoma;

4. Active infection (infection requiring IV antibiotics), including active tuberculosis, and known and declared HIV;

5. Pregnancy (absence confirmed by serum or urine β-HCG test) or lactation period;

6. Concurrent treatment with any other anti-cancer therapy;

7. Class 3-4 cardiac morbidity, as defined by the New York Heart association Criteria (e.g.

uncontrolled or symptomatic congestive heart failure, myocardial infarction within six months prior to the start of study, uncontrolled or symptomatic angina) and any cardiac condition, which in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient;

8. Current active hepatic or biliary disease (with exception of Gilbert’s syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment);

9. Renal function as measured by creatinine clearance <30 ml/min;

10. Presence of severe and/or uncontrolled concurrent medical disease (e.g. uncontrolled diabetes mellitus, uncontrolled liver disease, including chronic viral hepatitis judged at risk of reactivation, uncontrolled active infection such as HIV infection, etc.);

11. Concomitant (or within 4 weeks before randomisation) administration of any other experimental drug under investigation; chemotherapy or other anti-cancer therapy for the recurrence or metastatic disease; chemotherapy for initial treatment, i.e. chemoradiotherapy, is allowed, unless it has been stopped 3 weeks before inclusion.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-03-2009
Enrollment:	74
Type:	Anticipated

Ethics review

Positive opinion

Date:	03-09-2010
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL2399
NTR-old	NTR2507
Other	EudractCT : 2008-006415-20
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A