Phase I/II study of combined treatment with AT-101, cisplatin and radiotherapy in patients with locally advanced head and neck cancer

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Primary objective:The main objective of this study is to assess the feasibility, tolerability and the maximum tolerated dose (MTD) of oral AT-101 in combination with concurrent cisplatin-based chemotherapy and radiotherapy (RT) in advanced HNSCC, as...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON33661

Source
ToetsingOnline

Brief title
AT-101, cisplatin and radiotherapy in head and neck cancer

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
head and neck squamous cell carcinoma; head and neck cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: KWF Kankerbestrijding

Intervention

Keyword: Apoptosis, Bcl-2, Chemoradiotherapy, Head and neck cancer

Outcome measures

Primary outcome

Primary endpoint:

• Tolerability of combined treatment consisting of oral AT-101 and concurrent cisplatin-based chemoradiation, i.e. the definition of a feasible, safely administrable daily dose of oral AT-101, close to the MTD, in combination with standard chemoradiation.

Secondary outcome

Secondary endpoints:

• Identification of the Dose-Limiting Toxicity (DLT)

• Incidence, intensity and reversibility of observed adverse events/reactions of AT-101 in combination with cisplatin-radiotherapy

• Study on translational research parameters:

- Determination of systemic and local (intratumoral/normal tissue) accumulation of cisplatin-DNA adduct formation, in white blood cells (WBC), buccal cells and primary tumor (if accessible)

- Immunohistochemical assessment of proteins involved in apoptotic response,

by analysis of baseline tumor and normal skin biopsies and repeated

on-treatment biopsies.

- In vivo detection of apoptosis, using 99mTc-Annexin V scintigrapghy, at

baseline and during treatment

• Pharmacokinetics of AT-101

• Document anti-tumor effects of combined modality treatment, according to

RECIST criteria

Study description

Background summary

Despite significant improvements in the treatment of patients with inoperable head and neck cancer, recurrence rates remain a major obstacle. Thus, there is a clear need to develop new therapeutic approaches to further enhance the anti-tumor efficacy of existing standard regimens, such as cisplatin-based chemoradiotherapy. Overexpression of anti-apoptotic members of the Bcl-2 family is frequently observed in HNSCC and has been associated with resistance to radio- and chemotherapy and poor prognosis.
From structure-studies and binding assays, it was shown that AT-101 is a potent inhibitor of the anti-apoptotic proteins Bcl-2, Bcl-XL, and Mcl-1. In experimental and preclinical studies, AT-101 demonstrated pro-apoptotic properties in a dose dependent manner, with selective cytotoxic activity towards malignant cells. It has shown limited antitumor effects when used as single agent after oral administration and preliminary evidence of efficacy when combined with docetaxel in HRPC. However, after concurrent administration of AT-101 with radiation or cisplatin-chemotherapy the anti-proliferative effects were significantly enhanced in preclinical experimental studies.
Because AT-101 is able to enhance both radiation- and chemotherapy-induced tumor regression, it is an attractive drug for concomitant use with concurrent cisplatin-based chemoradiotherapy. From preclinical studies and phase I clinical data it can be concluded that oral administration of (±)-Gossypol and AT-101 are well tolerated.
For this study oral administration of AT-101, concurrently with 3-weekly cisplatin i.v. and radiation is proposed to allow optimal interaction. Two schedules of AT-101 will be tested in parallel: First, daily administration of AT-101 for two weeks, every 3 weeks will be tested in a dose-escalating manner. Second, a pulse dose regimen of oral administration of AT-101 will be

given, consisting of 3 consecutive days of oral AT-101 BID, every 3 weeks. The administration of cisplatin, concurrently with radiation is standard practice in HNSCC.
Because there are no safety data on concurrent administration of AT-101 and cisplatin-based chemoradiation in patients with advanced solid tumors, it is necessary to evaluate tolerability and toxicity prior to initiation of phase II-III studies. Toxicity profiles of AT-101, cisplatin and radiation do not show substantial overlap, and therefore a combined approach is justified. In order to be able to fully understand the pro-apoptotic properties of AT-101, the first group of patients will be treated without AT-101, with concurrent chemoradiation only. This will enable us to investigate changes in the biomarkers from the translational research, relative to baseline values, i.e. without the addition of AT-101. The starting dose of oral AT-101 at 10 mg/day is based on previous experience within phase I studies and preclinical data. Dosages will be subsequently increased in a dose-escalating manner.

Study objective

Primary objective:

The main objective of this study is to assess the feasibility, tolerability and the maximum tolerated dose (MTD) of oral AT-101 in combination with concurrent cisplatin-based chemotherapy and radiotherapy (RT) in advanced HNSCC, as a guidance for the recommended dose in future studies.

Secondary objectives:

Additional objectives include the exploration of mechanisms, involved in the therapeutic effect of the different modalities in this combined modality treatment, exploration of pharmacokinetics of AT-101, and documentation of therapeutic effects.

Study design

This is a single center, uncontrolled phase I/II dose-escalation combination study with a sequential group design using 2 parallel schedules of AT-101. Treatment will consist of a fixed regimen of concurrent cisplatin-based chemoradiation and dose-escalated AT-101. RT will be given to a total dose of 70 Gy in 35 fractions in an overall treatment time of 7 weeks. Cisplatin will be given 3-weekly intravenously (i.v.), 100 mg/m2, 1-2 hour before RT, for a total of 3 courses, with additional hydration. AT-101 will be according to two parallel schedules as defined below.

1. In the first schedule, AT-101 will be given daily orally 4 hours before RT in a dose escalating manner, for 2 weeks every 3 weeks on radiation-treatment days only. Courses will begin on cisplatin dosing days (days 1, 22, and 43). A

run-in period of 1 week of AT-101 alone will used before chemoradiation is started, without delaying the start of chemoradiation.

2. In the second, parallel schedule, pulse dose of AT-101 is given, using higher doses of AT-101 on 3 consecutive days, every 3 weeks. In this schedule, no run-in period with AT-101 alone is used.

Starting Dose of AT-101
The starting dose of AT-101 will be 0 mg po daily. This will represent the population of 3 patients within the two parallel groups with baseline values for the biomarker studies. There will be no delay in enrollment between this dose level and the first dose levels that include AT-101.
In the daily administration group, the initial patients treated with AT-101 will receive a dose of 10 mg po daily. In the pulse dose group, the initial patients treated with AT-101 will receive a dose of 20 mg BID for 3 days orally. Enrollment into this group will proceed in parallel to enrollment into the daily administration group.

Methods and Endpoints
The rate of subject entry and escalation to the next dose level will depend upon assessment of the safety profile of patients entered at the previous dose level. There will be no delay in enrollment between dose level 0 and subsequent dose groups, as dose level 0 does not include the investigational product. Toxicity will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. A minimum of three patients will be entered on each dose level. Decision on further escalation will be made no sooner than 4 weeks after completion of a dose level and will be based on the toxicity assessment in that first cycle and the documentation of any DLT (for definitions see below). Patients will be enrolled separately in the two parallel groups, i.e. when the required number of patients has been entered in a dose level, the next eligible patient will be entered in the parallel study using the above stated guidelines for subsequent enrolment and expansion into the new cohort.

Study burden and risks

Extent of burden comprises:

- additional questions during routine follow up pertaining to toxicity
- additional blood sampling for pharmacokinetics: 14 vena punctures.
- 2 skin biopsies

There is a strong need for more effective therapeutic strategies for locally advanced head and neck cancer. Given recent insights into mechanisms of treatment resistance and the availability of novel targeted agenst, the testing of new combined modality approaches is of pivotal importance. The toxicity profile of the study medication is known and acceptable and does not overlap

with that of standard chemoradiotherapy, justifies the extra (minimal) burden to the patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Histologically proven squamous cell carcinoma of the head and neck
• Oral cavity, oropharyngeal, or hypopharyngeal carcinoma
• Inoperable TNM stage III/IV, M0
• Patient must have measurable disease
• Age > 18 years
• Performance status WHO 0-2
• No prior r adiation therapy to head and neck region
• No prior cisplatin-based chemotherapy

• Adequate laboratory results:
- WBC > 4.0 x 10E9/l
- platelets > 100 x 10E9/l
- calculated or 24 hour creatinine clearance > 50 ml/min
- ASAT/ALAT < 2.5 times upper limit of normal range
- Bilirubin < 1.5 x upper limit of institution's normal range
• Willingness to use contraception by a method that is deemed effective by the Investigator throughout the treatment period and for at least 30 days following the last dose of therapy
• Willing and able to undergo blood sampling for pharmacokinetics
• Signed written informed consent before entry into study.
• Entry criteria for translational research:
- Willing and able to undergo blood sampling, harvesting of buccal smears and tumor biopsy (mandatory)
- Willing and able to undergo skin biopsy and nuclear scanning (optional)

Exclusion criteria

• Breast feeding or pregnancy
• Uncontrolled arrhythmia
• Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, ulcerative colitis, inflammatory bowel disease, or partial or complete small bowel obstruction
• Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.
• Known active symptomatic fungal, bacterial and/or viral infection including active HIV
• Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending

Start date (anticipated):	01-01-2009
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	AT-101 (R-(-)-gossypol acetic acid)
Generic name:	R-(-)-1,1', 6,6',7,7'-hexahydroxy-3,3'-dimethyl-5,5'bis(1-methylethyl)[2,2'-binaphtalene]-8,8'-dicar
Product type:	Medicine
Brand name:	cisplatin
Generic name:	cisplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-01-2009
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-02-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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
EudraCT	EUCTR2007-006120-36-NL
CCMO	NL24263.031.08