Olaparib dose escalation trial in patients treated with radiotherapy for laryngeal and oropharyngeal squamous cell carcinoma

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To define the maximal tolerated dose (MTD) of olaparib in combination with radiotherapy in laryngeal and oropharyngeal SCC.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON43772

Source
ToetsingOnline

Brief title
Olaparib and radiotherapy in Head and Neck cancer

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Head and Neck Cancer, squamous cell cancer of Head and Neck

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut

Source(s) of monetary or material Support: Astra Zeneca,Financiele grant van AstraZeneca

Intervention

Keyword: Head and Neck cancer, Olaparib, Radiotherapy

Outcome measures

Primary outcome

The incidence of dose limiting toxicities

Secondary outcome

1)Toxicity and safety variables

- Acute toxicity: severity, duration and relation with treatment of all adverse events according to CTCAE version 4.03 occurring from start of treatment until 3 months after end of treatment

- Late toxicity: severity, duration and relation with treatment of possibly, probably or definitely related adverse events according to CTCAE version 4.03 occurring from 3 months after end of treatment until 2 years after end of treatment

- Swallowing function preservation at 1 year

- Tube feeding dependency at 1 year

2) PK variables of olaparib (steady state AUC, steady state C-max, steady state C-min)

3) Pd variables (PARP inhibition in PBMCs)

4) Variables assessing efficacy of the study treatment:

- Objective response rate at 12 weeks after end of treatment

- Locoregional control defined as absence of (pathologically confirmed)

residual or recurrent tumor at primary site and in regional lymph node areas

- Localisation of recurrences in relation to the planned radiotherapy fields:

(boost) PTV

- Progression free survival at two years after end of treatment

Study description

Background summary

Accelerated, normofractionated radiotherapy is the treatment of choice in stage II-III laryngeal and oropharyngeal squamous cell carcinoma (SCC). However, twenty to thirty percent of patients with stage II-III laryngeal and HPV negative oropharyngeal SCC develop disease progression, mainly due to lack of locoregional control. Radiosensitizers such as cisplatin and cetuximab are added to radiotherapy in more advanced stage of head and neck (H&N) cancer. These radiosensitizers improve loco-regional control and overall survival. Unfortunately, as these radiosensitizers, notably cisplatin, also dose intensify the radiation dose in normal tissues, they also significantly increase toxicity. Adding a more tumor-specific radiosensitizing agent could improve loco-regional control and overall survival without significantly increasing toxicity.

Radiotherapy kills tumor cells by inducing DNA damage. The efficacy of radiotherapy is limited by the ability of tumor cells to repair this DNA damage. Poly(ADP-ribose)polymerase (PARP) is an essential enzyme in base excision repair and single strand break DNA repair, DNA lesions arising from radiation treatment. PARP inhibition and consequently the inhibition of PARP-facilitated DNA repair enhances the anti-tumor activity of radiotherapy, as shown in preclinical studies including head and neck xenograft studies. This radiosensitization is thought to be proliferation dependent and is more pronounced in homologous recombination (HR) deficient cells, providing an opportunity for tumor specific targeting. Genetic analyses suggest that HR deficiency is commonly found in H&N SCC: ATM loss has been reported in 60% of human H&N SCC biopsies and FANC-F defects were reported in 15-21% of human H&N SCC biopsies and cell lines.

The efficacy of radiotherapy is also limited by tumor hypoxia, as tumor hypoxia results in radioresistance. Some PARP inhibiting compounds increase tumor perfusion in xenograft models, thereby reducing hypoxia and specifically sensitizing tumor cells to radiotherapy. Hypoxia is commonly found in H&N SCC and a high pre-treatment hypoxic fraction in H&N SCC tumors is associated with

worse outcome. The high prevalence of both hypoxia and HR deficiencies in H&N SCC support the concept of tumor-specific radiosensitization by PARP inhibition in head and neck cancer patients.

Olaparib is a potent PARP inhibitor developed as an anti-cancer drug for HR defected tumors and as a dose intensifier for chemo- and radiotherapy. In humans, olaparib has a low toxicity profile as a single agent, with increasing bone marrow toxicity when combined with chemotherapy. The combination of olaparib and radiotherapy for H&N SCC is expected to improve locoregional control and thereby overall survival. However, this combination treatment has never been tested in humans before. The purpose of this study is to determine the safety and tolerability of radiotherapy for laryngeal and orophagyngeal SCC with concurrent olaparib.

Study objective

To define the maximal tolerated dose (MTD) of olaparib in combination with radiotherapy in laryngeal and oropharyngeal SCC.

Study design

This is an open-label, dose-escalating, non-randomized, single-centre phase I study of olaparib administrated orally once daily combined with radiotherapy for laryngeal and oropharyngeal squamous cell carcinoma. All patients receive the same radiotherapy regimen with dose escalation of olaparib. Dose escalation is performed using a time-to-event continuous-reassessment-model (TITE-CRM) design.

Intervention

Radiotherapy (standard treatment): Radiotherapy will be given with conventional fractionation schedule, Five fractions per week will be given. Overall radiotherapy treatment time will be 7 weeks. According to NKI-AVL policies, either a sequential boost or simultaneous integrated boost (SIB) technique will be used.

Olaparib (experimental treatment): The pre-defined dose levels of olaparib are 25mg QD and 50mgQD. Olaparib will be taken orally once daily starting one week before radiotherapy. In dose level 1 (25mgQD) olaparib will be taken in the morning at a fixed time point (week -1) and will continue during the first four weeks of radiotherapy including the weekends but will be taken in the evening before treatment. In dose level 2 (25mgQD) the same intake scheme will be done but during the complete radiotherapy treatment of 7 weeks. In dose level 3 (25mg QD) and level 4 (50mg QD) olaparib will be taken orally in the morning at a fixed time point starting one week before RT. And during radiotherapy days

1.5 to 2 hours before radiotherapy, excluding the weekends.

Study burden and risks

Patients will experience the side effects of the standard RT regimen and above that potentially side-effects induced by the addition of olaparib. The possible risks are the increase of radiation side effects, especially skin reaction, mucositis and fibrosis. Other side effects are unknown and purpose of this study.
During one day the patient is admitted to the hospital for pharmacokinetic analysis. During the total participation of the trial over a period of one year, at 18 unique instances blood samples will be collected for safety (12 instances) and research (10 instances) purposes. During a regularly planned tumor biopsy, an extra biopsy sample will be taken for research purposes.

All patients in this trial will have two standard MRI exams, one at baseline and one during the first week of olaparib only treatment. In patients with oropharynx carcinoma, we will use the regularly planned diagnostic MRI at baseline; the second MRI and both MRIs in patients with larynx carcinoma will be made for research purposes only. In the standard MRI exam 15 ml of the contrast agent Dotarem (Gadoteric acid, concentration 0.5M) is administered intravenously. No adverse effects are known of the administration of a second dose one week after the regular exam. The repeat of the MRI exam causes a negligible risk for the patient.

During the first 3 months after end of the radiation treatment patients will be seen more frequently for follow visits compared to standard treatment.

In this study, the analysis of tumor and germline DNA through NGS is optional. If patients take part in this analysis, there is a possibility of detection of unsolicited findings, i.e. germline DNA variants that confer an increased risk of developing malignancies or other diseases both for the patient and his/her family. Patients will be informed about this possibility, and will be offered genetic counseling in case of revelation of a variant which is clinically relevant and medically actionabl.

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

1. >=18 years of age
2. Histologically confirmed squamous cell carcinoma of the larynx (T2N0M0 or T1-2N1-2bM0 or T3N0-2bM0 or patients with locally advanced disease who will not receive concurrent chemotherapy) or histologically confirmed squamous cell carcinoma of the oropharynx (T1-2N1-2bM0 or T3N0-2bM0 or patients with locally advanced disease who will not receive concurrent chemotherapy)
3. In case of oropharyngeal carcinoma: tumor HPV status negative, or history of smoking >= 10 pack years
4. WHO performance 0-1
5. Life expectancy of at least 6 months
6. Adequate hematological, renal and hepatic functions
a. Hemoglobin >= 6.2 mmol/L
b. Leucocytes >= 3.0 x 10E9/L
c. Absolute neutrophil count >= 1.5x10E9/L
d. Platelet count >= 100 x 10E9/L
e. Total bilirubin <= 1.5 x UNL
f. ASAT/ALAT <= 2.5 x UNL
g. Creatinine clearance >= 50 ml/min; measured using a 24-hours urine sample or calculated using the Cockcroft-Gault formula
7. Evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 21 days of study treatment. Non-childbearing potential or

postmenopausal is defined as:
• Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
• LH and FSH levels in post menopausal range for women under 50 years of age
• Radiation-induced oophorectomy with last menses > 1 year ago
• Chemotherapy-induced menopause with > 1 year interval since last menses
• Surgical sterilisation (bilateral oophorectomy or hysterectomy)
8. Patients of reproductive potential must agree to practice two effective medically approved contraceptive method during the trial and 3 months afterwards
9. Signed written informed consent.

Exclusion criteria

1. Concurrent active malignancy other than localized, non-melanoma skin cancer or carcinoma-in-situ of the cervix (unless definitive treatment was completed 3 years or more before study entry and the patient has remained disease free)
2. Anti-cancer therapy including chemotherapy, radiotherapy, endocrine therapy, immunotherapy or use of other investigational agents within the 3 weeks prior to start of therapy (or a longer period depending on the defined characteristics of the agents used e.g. 6 weeks for mitomycin or nitrosourea). Patients may continue the use of LHRH agonists for cancer; bisphosphonates for bone disease and corticosteroids.
3. Major surgery within two weeks of starting study treatment.
4. Participation in other trial with investigational drug or treatment modality
5. Gastrointestinal disorders that may interfere with absorption of the study drug or patients who are not able to take oral medication.
6. Tube feeding before the start of treatment.
7. Prior radiotherapy to head & neck region.
8. Blood transfusion in the four weeks prior to study entry
9. Persistent toxicities (CTC >= grade 2) with the exception of alopecia, caused by previous cancer therapy
10. QT-interval >470 msec
11. Significant cardiovascular disease as defined by:
a. History of congestive heart failure defined as NYHA class III
b. History of unstable angina pectoris or myocardial infarction up to 3 months prior to trial entry;
c. Presence of severe valvular heart disease
d. Presence of a ventricular arrhythmia requiring treatment;
e. Uncontrolled hypertension
12. Patients considered a poor medical risk due to:
a. non-malignant systemic disease
b. active, uncontrolled infection requiring parenteral antibiotics
c. a serious, uncontrolled medical disorder; examples include, but are not limited to:
i. uncontrolled major seizure disorder
ii. unstable spinal cord compression
iii. superior vena cava syndrome
iv. extensive bilateral lung disease on HRCT scan

v. any psychiatric disorder that prohibits obtaining informed consent.
13. Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
14. Patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy.
15. Patients with known active hepatic disease (i.e. Hepatitis B or C)
16. Patients with myelodysplastic syndrome/acute myeloid leukaemia or features suggestive of MDS/AML on peripheral blood smear.
17. Concomitant medications:
a. Any previous treatment with a PARP inhibitor, including olaparib
b. Patients receiving the following classes of inhibitors of CYP3A4 (see paragraph 6.4.2 for guidelines and wash out periods)
- Azole antifungals
- Macrolide antibiotics
- Protease inhibitors
18. Breast-feeding women

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-09-2014
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Olaparib
Generic name:	Olaparib

Ethics review

Approved WMO Date:	09-07-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-02-2014
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2011-002963-79-NL
CCMO	NL38482.031.13

Study results

Results posted: 26-03-2024

First publication
26-03-2024