Sentinel lymph node (SLN) detection in oral cancer: a head to head comparison between 99mTc-Tilmanocept and 99mTc-Nanocoll

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Primary objective: The primary objective of this study is to compare the preoperative radiotracer kinetics (rate of injection site clearance and rate of SLN uptake) for Lymphoseek and 99mTc-Nanocoll. Secondary objectives: * To compare the number of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Head and neck therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON47858

Source
ToetsingOnline

Brief title
Lymphoseek (99mTc-Tilmanocept)

Condition

- Head and neck therapeutic procedures

Synonym
lymphatic metastasis, Sentinel lymph node biopsy

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: SpePharm AG - Norgine Ltd

Intervention

Keyword: lymph nodes, Lymphatic metastasis, mouth neoplasms, sentinel lymph node biopsy

Outcome measures

Primary outcome

The most important parameter of this pilot study is to compare the preoperative radiotracer kinetics (rate of injection site clearance and rate of SLN uptake) for Lymphoseek and 99mTc-Nanocoll.

Secondary outcome

Secondary objectives:

* To compare the number of lymphoscintigraphically detected SLNs identified by Lymphoseek and 99mTc-Nanocoll on a per-subject basis.

* To compare differences in the ratio of counts between Lymphoseek and 99mTc-Nanocoll for the hottest SLN relative to the primary peritumoral injection site.

* To compare patient pain tolerance (i.e., patient*s perceived level of discomfort) at the injection site for Lymphoseek and 99mTc-Nanocoll.

* To compare pathologic assessment (presence or absence of metastasis) of the excised lymph node(s) identified by Lymphoseek and 99mTc-Nanocoll on a per-subject basis.

* To compare the number of nodes localized at the early scan (0-4 hour) with the number of nodes localized on the late scan (20-26 hour).

* Observing contralateral drainage patterns in lateralized tumors and compare

these patterns between Lymphoseek and 99mTc-Nanocoll, especially in case of a

positive sentinel node

Study description

Background summary

The sentinel lymph node (SLN) procedure is a diagnostic staging procedure that is applied in a variety of tumor types, including head and neck squamous cell carcinoma (HNSCC). The procedure aims to identify the first draining lymph node(s), the SLN(s), which is most likely to harbor metastases. The histopathologic status of the SN should reflect the histopathologic status of the rest of the nodal basin, and additional treatment of the nodal basin (e.g., surgery) should be performed in case of metastatic involvement of the SLN. A negative SLN, however, would justify a wait and see policy concerning treatment of the nodal basin. In short, the routine SLN procedure consists of preoperative peritumoral injections of a 99m-technetium (99mTc)-labeled colloid followed by lymphoscintigraphy using planar or single photon emission tomography (SPECT) imaging. Based on the lymphoscintigraphy the position of the SLN is marked on the skin and intraoperative detection is possible by tumor injection of blue dye and by using a portable gamma probe (1).
Until now, most data showed that the combined dye and radioactive colloid approach reliably stages the clinically negative neck (cN0) in early stage oral cavity carcinoma (2,3,4). However, in floor of mouth (FOM) tumors, detection of the SLN is more difficult. This is probably due to the short distance between the primary tumor and the first draining lymph nodes (SLNs), which may be found in the submandibular region. In these cases, the resolution of the gamma- or SPECT camera is not always sufficient to visualize the SLN(s). The injection site (around the primary tumor) produces a large hotspot on lymphoscintigraphy possibly hiding SLN(s) in the close proximity of the primary tumor (*shine through* / *overshine*). As a result, second echelon lymph nodes may erroneously be considered as SLNs. On lymphoscintigraphy it is often difficult to differentiate hot spots between real sentinel nodes and second echelon nodes. In clinical practice probably too many lymph nodes are harvested because some hot spots will actually represent second echelon nodes. Extirpation of second echelon nodes may induce unnecessary morbidity and risk of complications.
Based on a multivalent strategy, Lymphoseek (99mTc-Tilmanocept) exhibits a high affinity for a lymphoid-specific receptor, which provides sustained SLN uptake without distal node accumulation (second echelon nodes).
Due to its rapid clearance from the injection site, rapid uptake and high retention within the first drainage lymph node (SLN), as well as low uptake by the remaining (higher echelon) lymph nodes Lymphoseek may be of benefit in floor of mouth tumors and other head and neck tumors with complex drainage

patterns and close spatial relation to the SLN: better visualization of SLNs close to the injection site and less hot spots in second echelon nodes.
The aim of the present pilot study is to evaluate the preoperative radiotracer kinetics of Lymphoseek and 99mTc-Nanocoll in sentinel lymph node biopsy in early oral cancer patients. This pilot study should be performed before designing a comparative study with sufficient number of patients to find an eventual difference in effectiveness between these tracers.

Study objective

Primary objective:
The primary objective of this study is to compare the preoperative radiotracer kinetics (rate of injection site clearance and rate of SLN uptake) for Lymphoseek and 99mTc-Nanocoll.

Secondary objectives:
* To compare the number of lymphoscintigraphically detected SLNs identified by Lymphoseek and 99mTc-Nanocoll on a per-subject basis.
* To compare the number of nodes localized at the scans at 2 time points for both tracers (0-30 minutes postinjection and 2-4 hours postinjection), to correlate the number of nodes with the late static scan (20h-26h postinjection) for the second agent and correlate these findings with the intraoperative findings.
* To compare differences in the ratio of counts between Lymphoseek and 99mTc-Nanocoll for the hottest SLN relative to the primary peritumoral injection site.
* To compare patient pain tolerance (i.e., patient*s perceived level of discomfort) at the injection site for Lymphoseek and 99mTc-Nanocoll.
* To compare pathologic assessment (presence or absence of metastasis) of the excised lymph node(s) identified by Lymphoseek and 99mTc-Nanocoll on a per-subject basis.
* To compare the number of nodes localized at the early scan (2-4 hour) with the number of nodes localized on the late scan (22-26 hour).
* Observing contralateral drainage patterns in lateralized tumors and compare these patterns between Lymphoseek and 99mTc-Nanocoll, especially in case of a positive sentinel node

Study design

This pilot study is a within-patient evaluation of radiotracer kinetics of Lymphoseek and 99mTc-Nanocoll for identification of sentinel lymph nodes in early stage oral cavity carcinoma.
The patients 1-10 will receive first the peritumoral injections with Lymphoseek with imaging as routinely done for the sentinel node procedure. 4-11 days later, the procedure will be performed routinely (so with Nanocoll). After these patients a team consisting of a nuclear physician, investigator and head

and neck surgeon will evaluate if the farmacokinetics of Lymphoseek result in lymphoscintigrams which are at least as good as the lymphoscintigrams of 99mTc-Nanocoll. When the imaging is at least as good as Nanocoll, patients 11-20 will receive the tracers in the opposite direction (so first Nanocoll + imaging, whereafter 4-11 days the SN procedure will be performed with Lymphoseek as radioactive agent).

Intervention

The intervention consists of the Lymphoseek injection 4-11 days before the standard procedure in the first 10 patients to compare the imaging between Lymphoseek and Nanocoll. However, after 10 patients and when the imaging of Lymphoseek will be considered as least as good as Nanocoll, the next 10 patients will receive the Nanocoll first and 4-11 days later the Lymphoseek as tracer for the SN procedure. The other aspects of the procedure will be unmodified.

Study burden and risks

Lymphoseek may identify SLNs more reliable than routinely used Nanocoll. The information obtained by lymphoscintigraphy may be helpful in harvesting the sentinel lymph node(s). The extra administration of 0.69mSv of the injection agent will result in an acceptable radiation burden to the patient, i.e., comparable to natural background level. Therefore we conclude the risk is negligible for this study.

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. The patient has provided written informed consent authorization before participating in the trial.
2. The patient has a diagnosis of primary oral squamous cell carcinoma that is anatomically located in: mucosal lip, buccal mucosa, lower alveolar ridge, upper alveolar ridge, retromolar gingival (retromolar trigone), floor-of-the-mouth, hard palate or oral (mobile) tongue, and is stage T1-T2, N0, M0 (see Appendix 3: TNM Staging).
3. Clinical nodal staging (N0) has been confirmed by negative results from ultrasound guided fine needle aspiration cytology within 30 days of the SLN procedure.
4. The patient is a candidate for transoral excision.
5. Patients with prior malignancy are allowed provided the patient meets both of the following criteria:
* Underwent potentially curative therapy for all prior malignancies and is deemed low risk for recurrence; and
* No malignancy for the past five years (except effectively treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix effectively treated with surgery alone or lobular carcinoma in situ of the breast treated with surgery alone), and no evidence of recurrence.
6. The patient is >18 years of age at the time of consent
7. The patient has an ECOG status of Grade 0 * 2 (see Appendix 4: Performance Status Criteria).

Exclusion criteria

1. The patient has a diagnosis of squamous cell carcinoma of the head and neck in the following anatomical areas: non-mobile base of the tongue, oropharynx, nasopharynx, hypopharynx, and larynx.
2. The patient is pregnant or lactating.
3. Patient is incapacitated

4. The patient has clinical or radiological evidence of metastatic cancer to the regional lymph nodes.
5. The patient has a history of neck dissection, or gross injury to the neck that would preclude reasonable surgical dissection for this trial, or radiotherapy to the neck.
6. The patient has had other nuclear imaging studies, including technetium 99m, conducted within 10 days (240 hours) of injection.
7. The patient is actively receiving systemic cytotoxic chemotherapy.
8. The patient is currently participating in another investigational drug trial or participated within 30 days prior to consenting.
9. Patient is on immunosuppressive, anti-monocyte, or immunomodulatory therapy.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-12-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lymphoseek
Generic name:	99mTechnetium-Tilmanocept
Product type:	Medicine
Brand name:	nanocoll
Generic name:	human albumin nanocolloid

Ethics review

Approved WMO Date:	02-05-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-08-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2017-000512-42-NL
CCMO	NL58099.041.17