Anti-cancer drugs and their effect on the ubiquitin cycle

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Ethical review	Approved WMO
Status	Pending
Health condition type	Leukaemias
Study type	Observational invasive

Summary

ID

NL-OMON31019

Source
ToetsingOnline

Brief title
Anti-cancer drugs and their effect on the ubiquitin cycle

Condition

- Leukaemias
- Lymphomas non-Hodgkin's B-cell

Synonym
cancer, hematologic malignancies

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: KWF/Nederlandse Kankerbestrijding

Intervention

Keyword: anthracyclins, histones, proteasome inhibitors, ubiquitination

Outcome measures

Primary outcome

To decipher the effect of anthracyclins on the ubiquitin cycle in living cells

and to decipher the biological reason for the effect on uH2 by both

anthracyclins and proteasome inhibitors, and both drugs in combination.

Secondary outcome

For the clinical part of the research project the effect of anthracyclines

and/or proteasome inhibitors on histone de-ubiquitination as observed in vivo

after administration of these drugs, will be correlated with outcome of the

patients (response to treatment and progression-free survival).

Study description

Background summary

Doxorubicin, a topo-isomerase II inhibitor, is used for a wide variety of cancers such as acute leukemia and (non-) Hodgkin's lymphoma. At present it is unclear whether topo-isomerase inhibition is the only mode of action of these drugs. We have found that anthracyclins, similar to the proteasome inhibitor bortezomib, can have an effect on the ubiquitin cycle. Although the action of the drugs is different, they both change the ubiquitin (Ub) modification of histones. This modification is critical in processes like gene silencing, DNA repair, chromatine packing and cell survival. We have already deciphered the mechanism employed by proteasome inhibitors to de-ubiquitinate histones. How doxorubicin is affecting H2 ubiquitination and the consequences for tumoour therapy are unknown and will be studied here. Theoretically, these drugs would also be very effective when used in combination.

Study objective

1. To decipher the biological basis underlying the alterations in

ubiquitination of histones in response to anthracyclines and proteasome inhibitors.
2. to find out whether the combined use of anthracyclines and proteasome inhibitors has additive or synergistic activity on histone de-ubiquitination.
3. to correlate changes in histone ubiquitination with response to treatment

Study design

From patients with hematological malignancies the ubiquitination of histones will be studied prior to and 4 hours after the administration of anthracyclines and/or proteasome inhibitors. These results will be correlated with clinical outcome (response to treatment and event-free survival).

Study burden and risks

The participating patients will be asked to donate 2 blood samples, directly prior to and 4 hours after the administration of anthracyclines and/or bortezomib. The blood will be collected from the already inserted intravenous canula which is used for the chemotherapy. There is no direct benefit for the patient but the burden and risks are minimal.
The healthy volunteers will only donate a baseline blood sample.

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. hematologic malignancy
2. treatment with anthracyclins and/or proteasome inhibitors

Exclusion criteria

prior treatment with either anthracyclins or proteasome inhibition

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2007
Enrollment:	110
Type:	Anticipated

Ethics review

Approved WMO
Application type: First submission

Review commission: METC Amsterdam UMC

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
CCMO	NL16467.018.07