24-Hour ambulatory blood pressure monitoring in patients with malignancies enrolled in phase I oncological studies

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

Summary

ID

NL-OMON32306

Source
ToetsingOnline

Brief title
ABPM in patients with malignancies

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer / hypertensie

Research involving
Human

Sponsors and support

Primary sponsor: Slotervaartziekenhuis
Source(s) of monetary or material Support: Nederlands Kanker Instituut

Intervention

Keyword: ABPM, blood pressure, malignancies, Phase I studies

Outcome measures

Primary outcome

Mathematical models will be fitted to the 24-hour blood pressure data.

Secondary outcome

not applicable

Study description

Background summary

In the past few years, novel anti-cancer agents have been introduced that are able to inhibit tumor growth by targeting the formation of new blood vessels (angiogenesis) of the tumor. It is hypothesized that if a tumor is no longer able to generate new blood support, it loses its ability to grow, and might even succumb altogether.[1] Drugs aimed at inhibiting the angiogenetic process have very specific pharmacological mechanisms of action (*targeted therapy*), and do not show the side-effects of the classical cytotoxic agents. However, elevated blood pressure (hypertension) is often observed and is treatment limiting. Although anti-hypertensive drugs often are able to treat the observed hypertension, in some cases the condition can become life-threatening (malignant hypertension) and lead to irreversible damage to eyes, kidneys, lungs and/or brains. Moreover, poorly controlled hypertension can lead to serious cardiovascular events, such as cardiac ischaemia and infarction.[2] These side-effects can cause some patients to stop drug treatment prematurely or continue on a lower dose, possibly resulting in decreased treatment efficacy. Several mechanisms are hypothesized to be involved in the occurence of this side effect, often involving vascular endothelial growth factor (VEGF).[3] In years to come, new inhibitors of the VEGF-transduction route will become available to the clinic that may also show hypertension as major side effect.[4] A good insight into, and -where possible- control of this side effect is therefore of significant importance. We aim to develop a pharmacokinetic-pharmacodynamic model for the relationship between antiangiogenic drug exposure and development of hypertension. When such a model is available, the model can be used to optimize dosing schedules to minimize the probability of developing hypertension, and to identify patients particularly at risk for this side-effect. It is known however, that the blood

pressure varies during the day in healthy subjects, in a periodic fashion (circadian rhythm). This obfuscates the PK-PD relationship, and a base signal describing these circadian fluctuations should therefore be included into the PK-PD model. As blood pressure and circadian variation in healthy volunteers most likely are not comparable to those of cancer patients, these data have to be recorded from the intented population, i.e. cancer patients.

Population pharmacokinetic-pharmacodynamic models incorporating the circadian rhythm built on 24-hour ambulatory blood pressure measurements (ABPM) have been described before in several populations, e.g. in patients with hypertension[5,6], but not yet in patients with cancer. These models generally consist of multiple sinusoidal functions. During the night, in most patients blood pressure decreases >10% as compared to daytime (dippers), while in some patients this decrease is not observed or even elevated blood pressures are observed (non-dippers). Generally, blood-pressures are elevated during the first few hours after arising, while throughout the day, external circumstances can alter blood pressure as well. Through measurement of ABPM a mathematical model of the circadian rhythm can be constructed, including both fixed effects (parameters describing the population mean behaviour) and random effects (e.g. interindividual variation in amplitude). The model can subsequently be used as a base signal for the PK-PD model for hypertension associated with anti-angiogenic therapy.

Study objective

The aim of the study is to obtain a profile of the circadian rhythm in blood pressure, in a representative population of cancer patients, thereby providing a base signal for the pharmacokinetic-pharmacodynamic model for hypertension associated with anti-angiogenic therapy.

Study design

Methodology
Monitoring will be performed using ABPM monitors, which are validated to international standards (British Heart Association / the American Association for the Advancement of Medical Instrumentation) and in routine use at the Slotervaart Hospital. All ABPM monitors will be calibrated, and programmed to record blood pressure readings every 30 minutes during the 24 hour cycle. Monitors will be placed on the patient*s non-dominant arm. Patients are instructed to keep the cuff and monitor on for 24 hours, and will be supplied with activity diaries for recording approximate sleep time, exertional event times and any other information pertinent to the study. It will be asserted by the investigator or nursing staff that the cuff is placed on the arm with an appropriate pressure, and that inflating the cuff does not present serious inconveniences to the patient. Also, upon installment of the device, two additional readings using a regular sphygmomanometer will be performed to

confirm the monitor is functioning.

Data recorded in the study will be converted to the appropriate data format by the investigator. Mathematical models are fitted to the blood pressure data using non-linear mixed-effets modeling software (NONMEM). Population parameters are estimated, as well as corresponding inter-individual variability descriptors. If possible, additional data provided by the patient such as sleep times and exertional activities will be incorporated in the model as covariates or in another appropriate statistical manner.

Study burden and risks

Burden:
Patients need to be equipped with a ABPM-device which monitors the blood pressure at preprogrammed intervals (each half hour). This can lead to minor inconveniences, such as localized increased pressure in the arm, or disturbance of sleep.

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

- enrolled in ongoing or future phase I studies of novel anti-cancer agents at the NKI-AVL
- scheduled to be hospitalized for at least a 24 hours during the phase I trial

Exclusion criteria

- currently associated with essential hypertension, cardiovascular disease or renal impairment
- currently treated with drugs that are known to have an effect on the cardiovascular and/or the renovascular system

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2008
Enrollment:	15
Type:	Anticipated

Ethics review

Approved WMO
Application type: First submission

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
CCMO	NL23093.031.08