Evaluating the safety of shortened infusion times for different oncological immunotherapies; An observational prospective study

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This study has been transitioned to CTIS with ID 2024-518878-14-01 check the CTIS register for the current data. Primary ObjectiveTo determine the incidence and grading of infusion related/hypersensitivity reactions reported per drug using the...

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

Summary

ID

NL-OMON51857

Source
ToetsingOnline

Brief title
MINUTE

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, lungcancer, melanoma (among others)

Research involving
Human

Sponsors and support

Primary sponsor: Isala Klinieken
Source(s) of monetary or material Support: Ministerie van OC&W,Bristol-Myers Squibb

Intervention

Keyword: Biologicals, Immunotherapy, Shortend infusion

Outcome measures

Primary outcome

Patient parameters:

• Weight

• Height

• Body Surface Area (m2)

• Sex

• Age

• Stage of disease

• Cancer type

Treatment parameters:

• Treatment with

Nivolumab/ipilimumab/Durvalumab/Bevacizumab/Atezolizumab/Trastuzumab

• Dose

• Infusion rate

• Number of infusions and treatment cycle

• Development of IRR

• Management of IRR

• Cycle of infusion where IRR is developed

• Grade of IRR

Secondary outcome

Standard clinical chemistry data for each mAb according to each mAbs standard

protocol

• Efficacy of treatment parameters (measured until end of study):

• Number of treatments needed

• Death

• Remission

• Progression

• Plasma levels of the administered mAb

• Patient reported experience measurements (PREMs)

Study description

Background summary

immunotherapy mAbs are highly effective, but can also cause infusion related hypersensitivity reactions. The occurrence of these reactions varies greatly between mAbs. Combination therapy with other drugs does influence the probability of an infusion reaction during a cycle. Most mAbs show a decrease in the incidence of IRRs but some mAbs show an increase in the incidence of IRRs in subsequent administrations. A higher infusion rate is associated with a higher likelihood for a reaction. Infusion related reactions are specified using the definition of Common Terminology Criteria for Adverse Events (CTCAE) criteria for: infusion related reaction. An infusion reaction usually starts within 30 to 120 minutes after start of administration.

The mechanism of the infusion related reactions is not concentration dependent, but mostly cause by cytokine release, caused by binding of the mAb to the target cell. in this way cytokines are released into the circulation causing symptoms.

Several measures can be taken to manage the infusion related reactions, such as a gradual increase of the dosage over the course of treatment, tapering the infusion time (for example 90-60-30 minutes), or using pre-treatment with antihistamines and corticosteroids. Due to the possibility of hypersensitivity reactions, all mAbs have restrictions on their rate of infusion, mostly determined during registration trials. However, it is known from earlier research, and pharmacologically expected, that infusion times can be shortened. For example, bevacizumab in 10 minutes had comparable incidence of IRRs to bevacizumab in 30 minutes

Based on this information we expect that mAbs can be infused in a shorter time (to around 10 -15 minutes per mAb% of the current infusion time). The advantages are the shorter hospital visits for patients, cost-effective home treatment and of course the amount of time saved for patients and nurses and finally increased capacity on the day-care facility. In Gil et al.5 a shortening of the infusion time to 10 minutes for Bevacizumab alone for just 73 patients created ¤17.960,30 nursing capacity per year. The waiting list for the Daycare Hospital Oncology Unit where these infusions were performed was also decreased. therefore the capacity of these facilities could be significantly improved.

It is suggested that mAbs are dosed on the top of their dose response curve¬38. This would explain why it is hard to establish a PK-PD relationship. As these drugs are structurally *over* dosed it would be possible to adapt different strategies to optimize dosing. The dosing of many monoclonal antibodies is currently based on a fixed dosing scheme, mostly based on Body Surface Area (BSA). Optimized dosing could potentially decrease the amount infusions with the monoclonal antibodies, thereby decreasing the (high!) costs of the treatment significantly. Another point is that is the stretching of the dosing intervals. As the extension of these dose intervals could lead to optimization of the patient*s time spend in the hospital for infusion, thus improving the quality of life. This would lead to a decrease of the burden for the oncology day care facility in Isala as well.

Study objective

This study has been transitioned to CTIS with ID 2024-518878-14-01 check the CTIS register for the current data.

Primary Objective
To determine the incidence and grading of infusion related/hypersensitivity reactions reported per drug using the definition of Common Terminology Criteria for Adverse Events (CTCAE) criteria for: infusion related reaction during accelerated infusion of mAbs, compared to historical matching cohorts.

Secondary objectives
• To evaluate the intra- and inter-individual variation in plasma levels of the

studied mAbs.
• Patient reported experience measures on the shortened infusion times.
• Health economic evaluation of the intervention

Study design

This study is an observational, explorative, prospective study to show whether shortening of infusion times for patients using nivolumab, pembrolizumab, trastuzumab, ipilimumab, durvalumab, atezolizumab continues to be associated with an acceptable safety profile.
The observational prospective study analysis from the medical records of demographics, anticancer drug use, adverse events and laboratory parameters are collected until end of treatment, death, or present time for patients.

The study is designed in two parts. In Part A, nivolumab, ipilimumab and pembrolizumab will be studied in three drug specific cohorts. Each drug specific cohort consists of a Run-In group involving 10 subjects and an Extension group of additional 82 subjects. In total 97 subjects will be included in each drug specific cohort. A total of 15 patients will be included, to account for fall out . For instance, due to disease progression.

Safety evaluations will be performed at least after completion of each Run In group (n=10). The evaluations will be performed by an independent institutional safety board.
Each extension group may only start after approval of the institutional safety board.

In Part B, 4 additional drugs will be studied in 4 drug specific cohorts, provided no serious adverse effects have occurred in part A, defined as no more than 2 subjects experienced infusion related reaction of grade 2 or higher. The selected drugs are bevacizumab, trastuzumab, durvalumab and atezolizumab. As in part A, in part B each drug specific cohort also consists of a Run-In group involving 10 subjects and an Extension group of additional 82 subjects. In total 97 subjects will be included in each drug specific cohort. Again, 15 patients will be included, to account for fall out.

Study procedure per patient
Patients start with standard of care. Standard of care is 100% of the infusion time as recommended by the SMPC. The aim of this period is to identify patients that develop IRRs and to prevent them from continuing onto the intervention procedure. Patients may continue, if during standard of care no IRR of grade 2 or higher has occurred. Before continuing to the intervention period of the study we evaluate the safety, as during the intervention period the infusion times will be shortened according to table 9.
During the intervention period the infusion times will be shortened as stated in table 9. During every cycle the SMPC infusion time is reduced with 50%, until a minimum infusion time of 10 minutes. If patients experience IRR during

the intervention part they will be treated for the IRR per protocol and excluded from the study.

All patients are 30 minutes observed after completion of the infusion during the complete course of the study.

For assessment of the pharmacokinetics of the different mAbs, through blood samples will be collected during cycle 2 to 4. Samples will be taken before the start of the next infusion. The Cmax samples will be taken during one of the cycles. One extra venapuncture is nessecary.
In the Run-In cohorts (n=10) during one cycle (preferably cycle 2) an additional blood sample will be collected after infusion to determine Cmax levels and clearance of each drug. No additional sampling will be performed during the other cycles.
Bioanalyses will be performed by a validated method in the laboratory of the pharmacy of the LUMC.

Study burden and risks

The risk-benefit analysis:
The possible risks of this study are additional blood sampling and infusion reaction that might occur due to fastened Immunotherapy cycles. The chance of excessive damage is nihil therefore it is considered a low-risk study as IRR on normal therapy is low and patients prone to IRR are not included in the study. The blood samples taken prior to infusion are not to be an excessive burden since no extra venepuncture is necessary. Foradditional blood sample will be collected after infusion to determine Cmax levels and clearance of each drug. An extra venepuncture is necessary to obtain these blood samples. These are not to be an excessive burden.

Group relatedness:
The group of patients receiving oncological immunotherapy are related to this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Starting, or already on treatment with monoclonal antibodies: nivolumab, pembrolizumab and ipilimumab, durvalumab, atezolizumab, trastuzumab and bevacizumab.
• 18 years and older.
• No known history of increased susceptibility to immunological reactions.
• Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.

Exclusion criteria

• Other research medication within 4 weeks of the start of the study.
• Inclusion in medical research in which the administration of medication should follow its stated times and dosages of infusions
• Dosage deviates from standard protocol

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):	01-02-2023
Enrollment:	0
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	HERCEPTIN
Generic name:	Trastuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	OPDIVO
Generic name:	Nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TECENTRIQ
Generic name:	Atezolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	YERVOY
Generic name:	Ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-03-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2024
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-07-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2024-518878-14-01
EudraCT	EUCTR2022-003669-39-NL
CCMO	NL83071.075.22