Phase I/II feasibility study combining Brentuximab Vedotin (Adcetris) with second line salvage chemotherapy (DHAP) in Hodgkin lymphoma patients refractory to first line chemotherapy or in first relapse who are eligible for high dose treatment followed by autologous peripheral blood stem cell transplantation

Published: 20-01-2014
Last updated: 25-04-2024

To increase the fraction of patients with a PET-negative metabolic complete remission after second line chemotherapy with 3 courses of DHAP , each in combination with one i.v infusion of BV. This will make more patients eligible for high dose...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas Hodgkin's disease
Study type	Interventional

Summary

ID

NL-OMON47390

Source
ToetsingOnline

Brief title
Transplant BRaVE

Condition

- Lymphomas Hodgkin's disease

Synonym
Hodgkin lymphoma, Lymphnode cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Millenium Pharmaceuticals

Intervention

Keyword: autologous stem cell transplant, Brentuximab Vedotin (BV), Hodgkin lymphoma, PET-negative metabolic complete remission, relapse / refractory

Outcome measures

Primary outcome

In the phase I study : to assess (severe) toxicity and determine the "

recommended dose level " to be applied in in the phase II part of the study (

Section 7.1.1 of the protocol).

In the phase II study : to assess the fraction of patients achieving a PET -

negative metabolic complete remission after 3 courses of BV + DHAP (Section

7.3.1 of the protocol) . The primary endpoint will thus be reached

approximately 3 months after the last patient has been enrolled in the phase II

study.

Secondary outcome

Phase I : (Section 7.1.2 of the protocol) : (S)AE's , time to hematologicical

recovery in the blood after each course of BV + DHAP , time to recovery from non - hematological toxicity , in particular neurotoxicity , after each course of BV + DHAP , incidence of dose modifications (dose reductions , prolongation of the interval between courses , premature termination of treatment) during the time the 3 courses are given , incidence of succesfull harvesting of an autologous stem cell graft after the 2nd course of BV + DHAP.
Phase II : (Section 7.3.4 in the protocol) : (S)AE's , time to hematological recovery in the blood , time to recovery from non - hematological toxicity , in particular neurotoxicity , after each course of BV + DHAP , incidence of modification of treatment (see above) , incidence of succesfull harvesting of an autologous stem cell graft , time to hematological recovery in the blood after ASCT , (S)AE's after ASCT.

Study description

Background summary

After 30 years of standard treatment of patients with relapse / refractory Hodgkin lymphoma there is an unmet need for a new treatment strategy which might improve the prognosis of this particular patient group. The introduction of the antibody-drug-conjugate Brentuximab Vedotin (BV) might play an important role in this situation.

Study objective

To increase the fraction of patients with a PET-negative metabolic complete remission after second line chemotherapy with 3 courses of DHAP , each in combination with one i.v infusion of BV. This will make more patients eligible for high dose chemotherapy with curative intend followed by autologous stem cell transplantation (ASCT) , which may ultimately lead to a higher chance for cure. It is not unlikely that this may lead to a new standard of care for this - young - patient population.

Study design

In the phase I part , dose - escalation in groups of 3 patients wil be applied with emphasis on toxicity (see scheme in the protocol - Section 5.1). Based on the results the optimal combination of BV + DHAP will be evaluated in a larger cohort of patients focussing on efficacy (phase II part of the study - Section 5.2).

Intervention

3 cyclus DHAP-Brentuximab followed by autologous peripheral blood stem cell transplantation

Study burden and risks

Because these patients have only been treated with one chemotherapy regimen before , no severe toxicity is expected by adding BV to DHAP. In heavily pretreated patients the toxicity profile of BV given as a single agent was acceptable. However , because of safety reasons a phase I part exploring dose - escalation will initially be done.
The risk for treatment - related mortality after high dose chemotherapy and autologous stem cell transplantation (ASCT) is since many years below 5%. This generally accepted percentage will - most likely - not change by adding 3 infusions of Brentuximab Vedotin (BV). In the light of a possible higher chance for cure the side effects cq the risks of the BV + DHAP combination treatment in this study are thought to be acceptable.

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

* Histologically confirmed CD30+ classical HL (central pathology review; results not required to enroll the patient in the study), primarily refractory to first line chemotherapy or in first relapse after any polychemotherapy regimen (e.g. ABVD, baseline BEACOPP or escalated BEACOPP, or other induction regimens)
* In case of relapse, the relapse must be histologically confirmed. In case histology is not possible, at least confirmation of the relapse by FNA is required.
* Measurable disease, as defined in Appendix C i.e. CT scans showing at least 2 or more clearly demarcated lesions with a long axis * 1.5 cm and a short axis diameter * 1.0 cm, or 1 clearly demarcated lesion with a long axis * 2.0 cm and a short axis diameter * 1.0 cm. These lesions must be FDG-positive
* Age * 18 years (upper age limit for auto-PBSCT at the discretion of the participating center)
* WHO * 2 (see appendix A)
* Life expectancy of > 3 months with treatment
* No major organ dysfunction, unless HL-related
* Total bilirubin < 1.5x ULN (unless due to lymphoma involvement of the liver or a known history of Gilbert*s syndrome; in that case ALT/AST may be elevated up to 5 x ULN)
* ALT/AST < 3x ULN (unless due to lymphoma involvement of the liver)
* GFR > 60 ml/min as estimated by the Cockroft&Gault formula (appendix D)
* Absolute neutrophil count * 1.5x109/L, unless caused by diffuse bone marrow infiltration by the HL
* Platelets * 100x109/L, unless caused by diffuse bone marrow infiltration by the HL
* Hemoglobin must be >8 g/dL
* Written informed consent
* Able to adhere to the study visit schedule and other protocol requirements
* Female patient is either post-menopausal for at least 1 year before the screening visit or surgically sterile or if of childbearing potential, agrees to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, or agrees to completely abstain from heterosexual intercourse.

* Male patients, even if surgically sterilized, (i.e., status post vasectomy) agree to practice effective barrier contraception during the entire study period and through 6 months after the last dose of study drug, or agrees to completely abstain from heterosexual intercourse.
* Eligible for high dose chemotherapy and autologous peripheral blood stem cell transplantation
* Resolution of toxicities from first-line therapy

Exclusion criteria

* Peripheral sensory or motor neuropathy grade * 2
* Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of PML
* Symptomatic neurologic disease compromising normal activities of daily living or requiring medications
* Patients who have been using other investigational agents within at least 5 half lives of the most recent agent used prior to enrollment in the study
* Patients who were treated with myelosuppressive chemotherapy or biological therapy * 4 weeks before study inclusion
* Female patients who are both lactating and breast feeding or have a positive serum pregnancy test during the screening period or a positive pregnancy test on Day 1 before first dose of study drug or adults of reproductive potential who are not using effective birth control methods.
* Patients with any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to first study drug dose
* Patients who have a history of another primary malignancy less than 3 years before study inclusion or previously diagnosed with another malignancy and have evidence of residual disease, with the exception of non-melanoma skin cancer, completely resected melanoma TNMpT1 and carcinoma in situ of the uterine cervix
* Patients with known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin.
* Patients with known HIV seropositivity, known hepatitis B surface antigen-positivity, or known or suspected active hepatitis C infection
* Patients receiving radiation therapy within 8 weeks prior to start of protocol treatment. Emergency radiation therapy is allowed, as long as measurable disease (at non-irradiated sites) persists.
* Patients with a serious psychiatric disorder that could, in the investigator*s opinion, potentially interfere with the completion of treatment according to the protocol
* Patients who have any severe and/or uncontrolled medical condition or other conditions that could affect their participation in the study such as:
* unstable angina pectoris, symptomatic congestive heart failure (NYHA II, III, IV), myocardial infarction * 6 months prior to first study drug, serious uncontrolled cardiac arrhythmia, cerebrovascular accidents * 6 months before study drug start
* severely impaired pulmonary function as defined as spirometry and DLCO (diffusing capacity of the lung for carbon monoxide) that is 50% or less of the normal predicted value and/or O2 saturation that is 90% or less at rest on room air

* any active (acute or chronic) or uncontrolled infection/disorders that impair the ability to evaluate the patient or for the patient to complete the study
* nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by this study drug, such as severe hypertension that is not controlled with medical management and thyroid abnormalities when thyroid function cannot be maintained in the normal range by medication

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):	28-04-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Adcetris
Generic name:	Brentuximab vedotin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cytarabine
Generic name:	Cytarabine

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-01-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-01-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	13-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2018
Application type:	Amendment
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
EudraCT	EUCTR2012-003097-45-NL
CCMO	NL40688.018.13