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A phase III study to determine the role of a second autologous stem cell transplant as consolidation therapy in patients with relapsed multiple myeloma following prior high dose chemotherapy and autologous stem cell rescue

Submission date
26/10/2006

Recruitment status
No longer recruiting

Registration date
26/01/2007

Overall study status
Completed

Last Edited
25/10/2022

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-a-second-stem-cell-transplant-for-people-whose-myeloma-has-come-back-following-a-previous-transplant

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2006-005890-24

IRAS number

ClinicalTrials.gov number
NCT00747877

Secondary identifying numbers
HM05/7287

Study information

Scientific Title
A phase III study to determine the role of a second autologous stem cell transplant as consolidation therapy in patients with relapsed multiple myeloma following prior high dose chemotherapy and autologous stem cell rescue

Acronym
Myeloma X Relapse (Intensive)

Study objectives
The primary aim of the study is to determine whether a high-dose procedure with autologous transplant is superior to low-dose consolidation therapy following re-induction chemotherapy in terms of time to disease progression.

Secondary aims are to determine:
1. Response rates to bortezomib, dexamethasone and adriamycin (PAD) in patients relapsing with myeloma following a previous autograft
2. Whether overall response rates following high-dose chemotherapy (with an autologous stem cell transplant) differs to those with low-dose consolidation therapy
3. Overall survival in both treatment groups
4. The feasibility of stem cell collection at relapse
5. The impact of the two treatment strategies on Quality of Life (QoL)

As of 15/02/2011 the anticipated end date was updated from 01/09/2011 to 01/04/2012.

Please note that as of 04/01/2013, the anticipated end date for this trial was updated from 01/04/2012 to 30/11/2016. Please also note that recruitment was completed on 21/11/2012.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Added 24/08/2007: West Glasgow Ethics Committee 1on 03/07/2007 (ref: 07/S0703/66)

Study design
Randomised, multicentre, open labelled, parallel group phase III trial (with single intervention registration phase).

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Relapsed Multiple Myeloma

Interventions
Interventions amended as of 24/08/2007:

All registered patients will receive 2 to 4 x 21 day cycles of PAD (bortezomib, doxorubicin and dexamethasone):

Bortezomib 1.3 mg/m2 on days 1, 4, 8 and 11 of each cycle via intravenous bolus
Doxorubicin 9 mg/ m2 on days 1 to 4 of each cycle via continuous intravenous infusion
Dexamethasone 40 mg/day on days 1 to 4, 8 to 11, 15 to 18 for cycle 1 and days 1 to 4 for cycles 2 to 4, orally

Patients who undergo Peripheral Blood Stem Cell (PBSC) mobilisation and harvest will receive:

Cyclophosphamide 1.5 to 3 mg/m2 on day 0 via intravenous infusion
Granulocyte-Colony-Stimulating Factor (G-CSF) 5-10 microgram/kg/day from day 1 to time of harvest via subcutaneous

Patients who undergo randomisation will be allocated to receive:

High-dose melphalan 200 mg/m2 on day 0 via intravenous infusion

OR

Low dose cyclophosphamide 400 mg/m2 weekly for 12 weeks, orally

Interventions provided at time of registration:

Registration:
All patients will receive two to four cycles of PAD (bortezomib, dexamethasone and adriamycin).

Peripheral Blood Stem Cell (PBSC) mobilisation:
Stem cells will be mobilised using cyclophosphamide, if stored cells are available from a previous harvest, omission of this mobilisation step is permitted.

Randomisation:
Patients who meet the eligibility for randomisation will receive consolidation therapy with either:

1. High-dose melphalan therapy supported by re-infusion of autologous stem cells;
2. Low-dose cyclophosphamide-weekly.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Bortezomib, dexamethasone and adriamycin (PAD), cyclophosphamide, melphalan therapy.

Primary outcome measure
Primary outcome measures amended as of 24/08/2007:

Primary outcome measure is time to disease progression and is defined as time from randomisation to the consolidation part of the trial to first documented evidence of disease progression. Patients who die prior to documentation of disease progression will be censored in the analysis. Central analysis of blood and urine samples (and bone marrow if needed) will by monitored at regular internals (at least post-reinduction treatment, 100 days post autologous stem cell transplant/30 days post-end of cyclophosphamide weekly, annually thereafter and if clinically indicated) to assess response/progression. Disease progression and response rates will be determined according to the International Uniform Response Criteria for multiple myeloma.

Primary outcome measures provided at time of registration:

Time to disease progression

Secondary outcome measures
Secondary outcome measures amended as of 24/08/2007:

1. Response to PAD re-induction treatment will be determined according to the International uniform response criteria for multiple myeloma through central analysis of blood, urine and bone marrow aspirate (if complete response is indicated from local results).

2. Progression-free survival is defined as the time from randomisation to the consolidation part of the trial to first documented evidence of disease progression or death from any cause. Patients who do not progress will be censored at the last date they were known to be alive and progression free.

3. Overall survival is defined as the time from randomisation to the consolidation part of the trial to death from any cause or last follow-up.

4. The feasibility of stem cell collection will be determined by the satisfactory mobilisation of an adequate number of peripheral blood stem cells (greater than 10 CD34+ cells/µl blood) and the subsequent harvest of sufficient numbers of stem cells to support high-dose chemotherapy (greater than 2.0 x 109 CD34+ cells/kg).

5. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ-C30) and EORTC-myeloma module (EORTC QLQ-MY20), the Leeds Assessment of Neuropathic Symptoms and Signs: Self-complete (LANSS) pain scale and the Brief Pain

Inventory (short form) will be used to measure patient-assessed Quality of Life (QoL) and evaluate pain in detail. Questionnaires will be administered at baseline, post re-induction treatment, pre-randomisation (if greater than two weeks since the completion of questionnaires post re-induction treatment), 100 days post-randomisation, 6 months post-randomisation, 1 year post-randomisation and annually thereafter.

6. Toxicity and safety will be reported based on adverse events, as graded by Common Terminology Criteria for Adverse Events (CTCAE V3.0) and determined by routine clinical assessments at each centre. This will be assessed throughout the trial.

Secondary outcome measures provided at time of registration:

1. Response rate to PAD
2. Overall response rate following randomised treatments
3. Overall survival
4. Feasibility of stem cell collection
5. Quality of Life (QoL)
6. Toxicity and safety

Overall study start date
01/09/2007

Completion date
30/11/2016

Eligibility

Key inclusion criteria
Inclusion criteria amended as of 24/08/2007:

Registration:
1. Diagnosed with symptomatic (including non-secretory) Multiple Myeloma (MM) previously treated with standard chemotherapy and autologous transplantation
2. Requiring therapy for first Progressive Disease (PD) (where PD is determined according to the International uniform response criteria for myeloma. Patients previously immunofixation negative who are now immunofixation positive need to demonstrate a greater than 5 g/liter absolute increase in paraprotein to be eligible for inclusion)
3. Demonstrate PD requiring treatment at least 18 months from time of first transplant
4. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
5. Aged at least 18 years
6. Adequate full blood count within 14 days before registration:
a. Platelet count greater than or equal to 50 x 109/L
b. Absolute Neutrophil Count (ANC) greater than or equal to 1 x 109/L
7. Adequate renal function within 14 days before registration:
a. Creatinine clearance greater than or equal to 30 ml/min
8. Adequate hepatobiliary function within 14 days before registration:
a. Total bilirubin less than 2 x Upper Limit of Normal (ULN)
b. ALanine aminoTransferase (ALT) or ASpartate aminoTransferase (AST) less than 2.5 x ULN
9. Adequate pulmonary function within 14 days before registration:
a. No evidence of a history of pulmonary disease. If a history, then KCO/DLCO (Carbon Monoxide diffusion in the lung) greater than or equal to 50% and/or no requirement for supplementary

continuous oxygen
10. Adequate cardiac function within 14 days before registration:
a. Left Ventricular Ejection Fraction (LVEF) greater than or equal to 40% by ElectroCardioGram (ECG) or Multiple Gated Acquisition (MUGA) scan
11. If female and of childbearing potential, must have a negative pregnancy test (either serum or urine Human Choronic Gonadotropin [HCG]) within 24 hours prior to start of PAD therapy
12. Provided written informed consent

Randomisation:
1. Registered into the Myeloma X Relapse (Intensive) trial and received 2-4 cycles of PAD re-induction chemotherapy according to the protocol
2. Responded ([s]Complete Response [CR] or [VG] Partial Response [PR]) or have Stable Disease (SD), following PAD re-induction chemotherapy according to the International Uniform Response Criteria for myeloma
3. Adequate stem cell mobilisation defined as greater than or equal to 2 x 106 CD34+ cells/kg or greater than or equal to 2 x 108 Peripheral Blood Mononuclear Cells (PBMC)/kg available for transplantation (including cells stored from a previous harvest)
4. Adequate full blood count within 14 days before randomisation:
a. Platelet count greater than or equal to 50 x 109/L
b. ANC greater than or equal to 1 x 109/L
5. Adequate renal function within 14 days before randomisation:
a. Creatinine clearance greater than or equal to 30 ml/min
6. Adequate hepatobiliary function within 14 days before randomisation:
a. Total bilirubin less than 2 x ULN
b. ALT or AST less than 2.5 x ULN
7. Adequate pulmonary function within 14 days before randomisation:
a. No evidence of a history of pulmonary disease, or if a history then KCO/DLCO greater than or equal to 50% and/or no requirement for supplementary continuous oxygen
8. Adequate cardiac function within 14 days before randomisation:
a. LVEF greater than or equal to 40% by ECG or MUGA scan

Inclusion criteria provided at time of registration:

Registration:
1. Patients with Multiple Myeloma (MM) previously treated with standard chemotherapy and autologous transplantation that require therapy for progressive disease following plateau
2. Patients with progressive disease at least 18 months from time of first transplant
3. Measurable serum and/or urine paraprotein or serum free light chain assay
4. Performance Status (PS) zero to two (Eastern Cooperative Oncology Group [ECOG])
5. Aged at least 18 years
6. Written informed consent

Randomisation:
1. Registered into the Myeloma X Relapse Intensive trial
2. Response to re-induction chemotherapy (Complete Response [CR], Partial Response [PR], Minimal Response [MR] or Stable Disease [SD]), according to European group for Blood and Marrow Transplantation (EBMT) criteria
3. More than or equal to 2 x 10^8 Peripheral Blood Mononuclear Cells (PBMC)/kg or more than or equal to 2 x 10^6 CD34+ cells/kg available for transplantation (including cells stored from a previous harvest)

Participant type(s)

Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
320 at randomisation (approximately 460 at registration)

Total final enrolment
293

Key exclusion criteria
Exclusion criteria amended as of 24/08/2007:

Registration:
1. Received therapy for their relapsed disease other than local radiotherapy, therapeutic plasma exchange, or dexamethasone up to a maximum of 200 mg. (Radiotherapy since pervious transplant sufficient to alleviate or control pain of local invasion is permitted. Patients who have received hemi-body radiation or similar since previous transplant will not be eligible)
2. ECOG Performance Status 3-4
3. Greater than or equal to Grade 2 peripheral neuropathy within 14 days before registration
4. Known HIV or Hepatitis B/C seropositivity (testing is not required for the trial)
5. Use of any investigational drug within 4 weeks prior to registration, or scheduled to receive any investigational drug during the course of the study
6. Known resistance to combined bortezomib, doxorubicin and dexamethasone (PAD) therapy
7. Known history of allergy contributable to compounds containing boron or mannitol
8. Any medical or psychiatric condition which, in the opinion of the investigator, contraindicates the patient's participation in this study
9. Previous or concurrent malignancies at other sites, with the exception of appropriately treated localised epithelial skin or cervical cancer. Patients with remote histories (>5 years) of other cured tumours may be entered
10. Pregnant or breast feeding
11. Unwilling to use adequate contraception during the study and for 6 months after the end of the study treatment if female of childbearing potential, or male whose partner is a female of childbearing potential unless they are surgically sterile

Randomisation:
1. Received any therapy for their relapsed disease, other than local radiotherapy or protocol PAD treatment, prior to randomisation. (Radiotherapy sufficient to alleviate or control pain of local invasion is permitted. Patients who have received hemi-body radiation or similar since previous transplant will not be eligible)
2. Progressive disease, according to International Uniform Response Criteria for myeloma following PAD re-induction therapy or stem cell mobilisation
3. Any contra-indication to protocol treatment that would make the patient ineligible

Exclusion criteria provided at time of registration:

Registration:
1. Patients who have received therapy for their relapsed disease other than local radiotherapy, therapeutic plasma exchange or dexamethasone up to a maximum of 200 mg
2. Females of child-bearing potential without a negative pregnancy test, immediately prior to the start of PAD therapy and/or unwilling to use barrier contraceptive precautions throughout the study or who are pregnant or breast-feeding
3. Non-secretory MM
4. Performance status three to four (ECOG)
5. Platelet count less than 50 x 10^9/L within 14 days before enrolment
6. Absolute neutrophil count less than 1.0 x 10^9/L within 14 days before enrolment
7. Grade two peripheral neuropathy within 14 days before enrolment
8. Presence of severe irreversible renal, hepatic, pulmonary or cardiac disease such as:
a. Total bilirubin, Serum Glutamic Pyruvic Transaminase (SGPT)/ Serum Glutamic Oxalacetic Transaminase (SGOT) more than two times the upper limit of normal
b. Left ventricular ejection fraction less than 40%
c. Creatinine clearance less than 30 ml/min
d. Diffusing capacity of the Lung for Carbon Monoxide (DLCO) less than 35% and/or receiving supplementary continuous oxygen (O2)
9. Known Human Immunodeficiency Virus (HIV) or Hepatitis B or C seropositivity (obligatory testing is not necessary)
10. Use of any investigational drug within four weeks prior to enrolment, or any patients scheduled to receive any investigational drug during the course of the study
11. Resistance to bortezomib therapy
12. Patients who have a medical or psychiatric condition, which, in the opinion of the investigator, contraindicates the patients participation in this study
13. Previous or concurrent malignancies at other sites, with the exception of appropriately treated localised epithelial skin or cervical cancer. Patients with remote histories (more than five years) of other cured tumours may be entered

Randomisation:
1. Patients demonstrating progressive disease, according to EBMT criteria, following re-induction or stem cell mobilisation

Date of first enrolment
01/09/2007

Date of final enrolment
30/11/2016

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

Clinical Trials Research Unit
Leeds
United Kingdom
LS1 3EX

Sponsor information

Organisation
The Leeds Teaching Hospitals NHS Trust (UK)

Sponsor details
Department of Research and Development
6th Floor, Wellcome Wing
Leeds General Infirmary
Great George Street
Leeds
England
United Kingdom
LS1 3EX

Sponsor type
Hospital/treatment centre

Website
http://www.leedsteachinghospitals.com/

ROR
https://ror.org/00v4dac24

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK (UK)

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype

Other non-profit organizations

Location
United Kingdom

Funder Name
Chugai Pharma UK (UK) (unrestricted educational grant)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results				No	No
Results article	results	01/07/2014	10/04/2019	Yes	No
Results article	results	01/05/2013	10/04/2019	Yes	No
Results article	results	01/06/2016	10/04/2019	Yes	No
Results article	results	01/07/2016	10/04/2019	Yes	No
Plain English results			25/10/2022	No	Yes