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RESEARCH PROTOCOL

Bortezomib-bendamustine-melphalan vs high-dose melphalan in autologous hematopoietic stem cell transplantation for relapsed multiple myeloma – a single center retrospective cohort study

Project Manager
Thomas Silfverberg, MD. Center for Clinical Research Dalarna/Department of Medical Sciences, Uppsala University

Principal investigator
Kristina Carlson, MD, PhD. Ass Prof. of at the Department of Medical Sciences, Uppsala University, Uppsala

Scientific supervisor
Honar Cherif, MD, PhD. Ass Prof. of at the Department of Medical Sciences, Uppsala University, Uppsala

Entity responsible for the research
Department of Medical Sciences, Uppsala University, Region Uppsala

Bortezomib-bendamustine-melphalan vs high-dose melphalan in autologous hematopoietic stem cell transplantation for relapsed multiple myeloma – a single center retrospective cohort study

Thomas Silfverberg[1,2], Honar Cherif[1], Kristina Carlson[1]

[1] Department of Medical Sciences, Uppsala University, Uppsala, Sweden.
[2] Center for Clinical Research Dalarna, Uppsala University, Falun, Sweden

Short title

Bortezomib-bendamustine-melphalan vs melphalan for multiple myeloma

Introduction

Multiple myeloma is a chronic hematological malignancy that accounts for about 10% of all hematological cancers and 1% of all cancers in general.[1] High-dose chemotherapy with melphalan (HDM) followed by autologous hematopoietic stem cell transplantation (ASCT) has been a cornerstone in treating multiple myeloma for fit patients since 30 years.[2,3] In recent years, many novel agents, as well as old drugs with new indications, have been introduced for multiple myeloma and thus changed the induction treatment prior to ASCT. Although these novel agents has improved overall survival (OS) and progression free survival (PFS), the role of consolidation with ASCT remains intact.[4,5] Many different variations of conditioning regimens prior to ASCT has been tried but so far HDM remains the standard of care.[6] Many eligible patients with long response after first line ASCT (ASCT1) are treated with a second ASCT (ASCT2) in first relapse, although the duration of disease control is rarely as long after ASCT2.

Bortezomib is a proteasome inhibitor that has improved the induction treatment for multiple myeloma. It has been used in many induction combinations and has beneficial effects when combined with alkylating agents.[7] Bendamustine hydrochloride is a cytotoxic compound with alkylating and anti-metabolite properties with acceptable toxicity when used in multiple myeloma patients.[8,9]

Survey of the field

In 2010 the IMF study group published a phase 2 study with bortezomib 1 mg/m^2 x4 in combination with melphalan 200 mg/m^2 for multiple myeloma with a complete response rate of 32% and no increase in toxicity.[10] The study was followed by the phase 3 randomized multicenter IFM 2014-02 study which could not show superiority over HDM in terms of response rates, PFS or OS.[11] In a phase 2 trial, Gimsing and colleagues treated patients at first relapse after ASCT with HDM, with bortezomib and dexamethasone as induction and added bortezomib to HDM in conditioning for ASCT2. Interestingly there was no difference in time to next treatment (TNT) and PFS between the ASCT1 and ASCT2.[12]

In 2013 Mark and colleagues conducted a phase I trial which showed no increase in toxicity using escalating doses of bendamustine in combination with HDM and an overall response rate of 80% including 45% of the patients obtaining complete remission (CR).[13] Martino and colleagues treated 32 patients with a bendamustine and HDM before a second ASCT in as part of first line treatment. They reported higher overall response rates as well as PFS and OS after two years with acceptable toxicity.[14] In addition, a study published in 2019 of 12 patients with high-risk cytogenetics or failure to achieve CR after ASCT were treated with bendamustine 200mg/m^2 and HDM with no difference in hematological recovery (compared with HDM in ASCT1), CR rates increased from 42 to 75% and the one year PFS and OS was 67% and 83% respectively.[15] Recently, a 2019 phase II study investigated the efficacy and safety of bendamustine 225 mg/m^2 and HDM. The study had a CR rate of 51% and a median PFS of 45 months in relapsed/refractory patients and slightly better in newly diagnosed patients.[16] Both these agents did not show any significant increase in toxicity when combined with melphalan, adding to the motivation of investigating the combination as conditioning regimen for ASCT for multiple myeloma.

Based on published research results, the standard conditioning regimen for patients eligible for a second ASCT in the setting of relapsed multiple myeloma at Uppsala University Hospital (UUH) was changed to the combination bendamustine-bortezomib-melphalan (BBM) during the period of 1 Nov 2011 until 30 Oct 2018.

Research question

The aim of this retrospective cohort study is to evaluate the efficacy and safety of the conditioning regimen BBM and compare it to HDM in the setting of relapsed multiple myeloma.

Project outline

This project will evaluate the efficacy and safety of the conditioning regimen bortezomib-bendamustine-melphalan (BBM) in combination with autologous hematopoietic stem cell transplantation (ASCT) in relapsed multiple myeloma given from 2011 to 2018 at Uppsala University Hospital. This approach will be retrospectively compared to high dose melphalan (HDM) in the same setting in the years prior to, and following the BBM-period. Data on efficacy and safety data will be collected through systematic analysis of electronic medical records and data from the Swedish Cancer Registry if the medical records are insufficient.

Methods

Study design

This is a retrospective single center cohort study comparing the new conditioning regimen bortezomib-bendamustine-melphalan to standard high-dose melphalan. The data sources will be electronic medical records and prospectively collected data from the Swedish Cancer Registry. The comparison will be analyzed in two parts. First, each patient will be its own control, comparing time to next treatment (TNT) for the first ASCT (always HDM, referred to as ASCT1) and second ASCT (BBM or HDM, referred to as ASCT2), and compare the mean difference between the two cohorts. Secondly, we will compare the efficacy and severe adverse events of BBM and HDM at ASCT2.

Study population

About 50 consecutive patients, who were referred to UUH for a second ASCT after relapse in multiple myeloma following HDM and ASCT between 1 Nov 2011 and 30 Oct 2018 and who received conditioning with bortezomib-bendamustine-melphalan will be included in this study. As a control group, 25 consecutive patients who were treated with HDM prior to 1 Nov 2011 and 25 consecutive patients following 30 Oct 2018. The patients, both in the intervention group and control group will be identified through the local European Society for Blood and Marrow Transplantation (EBMT) registry at UUH.

UUH is the referral hospital for seven Swedish regions with a total population of 2 151 353 at Dec 31 2022, which constitutes roughly one fifth of the population of Sweden.[17]

Inclusion criteria

- Diagnosis of first relapse after previous ASCT for multiple myeloma according to the International Myeloma Working Group.
- Treated with a second ASCT (ASCT2) as part of second line treatment at UUH.
- Conditioning at ASCT2 with bortezomib-bendamustine-melphalan or high-dose melphalan only.

Exclusion criteria

- Two (double) ASCT in first line treatment
- Failure to meet the minimal dataset, defined as:
    - Date of ASCT1 and ASCT2
    - Date of start of induction treatment for relapsed myeloma prior to ASCT2
    - Medical records from hospitalization for ASCT2
    - At least one follow-up visit (unless early death before first follow-up visit)
    - Date of progression and first treatment of relapsed multiple myeloma after ASCT2

Data collection

Study data will be collected through systematic analysis of electronic patient records from UUH and all the hospitals referring patients to UUH and from the Swedish Cancer Registry. All severe adverse events (AEs) will be collected until day 100 after ASCT2 according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Procedures

Mobilization

Stem cells were mobilized using a combination of cyclophosphamide (2 g/m^2) and granulocyte-colony-stimulating factor (G-CSF) 5 micrograms/kg subcutaneously starting on day 6 until stem cell harvest.

Harvest

Harvest of hematopoietic stem cells were done by apheresis of peripheral blood before first ASCT. A minimum of 4.0x10^6 $CD34^+$ cells/kg were harvested and cryopreserved to meet the minimal requirement of 2.0x10^6 $CD34^+$ cells/kg per ASCT. No ex-vivo manipulation was made.

Conditioning

High-dose melphalan is given as a single dose of 200 mg/m^2 or 140 mg/m^2 if the glomerular filtration rate (GFR) is estimated below 30 ml/minute. There was a minimum wash-out time of 24 hours (48 hours if GFR <30 ml/minute) from the administration of melphalan and reinfusion of the autologous stem cells.

The BBM protocol consisted of bortezomib 1.3 mg/m^2 subcutaneously on day -5 and -2, bendamustine 100 mg/m^2 intravenously on day -3 and -2 and melphalan 200 mg/m^2 (or 140 mg/m^2 if the glomerular filtration rate is estimated below 30 ml/minute) intravenously on day -2. On day -2 bendamustine was administered first, followed by bortezomib and melphalan.

Anti-microbial prophylaxis

Ciprofloxacin was used to prevent bacterial infection during the neutropenic phase. Prophylaxis for herpes and Pneumocystis jiroveci were given for a minimum of three months. Patients who tested positive for HBs-ag (hepatitis B surface antigen) and/or anti-HBc (antibodies against hepatitis B core proteins) were given prophylaxis for hepatitis B-reactivation. No prophylaxis for fungal infection was given.

Supportive care

Intravenous hydration and allopurinol were administered at 300 mg/day day -5 to 0 as prophylaxis for uric acid nephropathy and to secure proper elimination of the chemotherapy. A minimum washout time of 24 hours (48 hours if GFR <30 ml/minute) was respected from administration of melphalan and reinfusion of the stem cells to minimize mutagenic pressure on the stem cells. Long acting granulocyte colony stimulating factor (G-CSF), mainly lipegfilgrastim, was administered as a standard on day +5 from 2017 and onwards to reduce the risk with and duration of the neutropenic period. All patients were given filtered and radiated blood products according to individual need until their lymphocytes exceeded 1.0 x 10^9/L. General administration of

antiemetics included netupitant, palonosetron on the first and fourth day of the conditioning and betamethasone daily during the conditioning including tapering after ASCT.

Endpoints

Primary endpoints

- Mean time to next treatment (TNT) after ASCT2 for BBM and HDM-treated patients
- Mean progression free survival (PFS) after ASCT2 for BBM and HDM-treated patients
- Mean TNT after ASCT1 and ASCT2 for each individual patient (each patient as its own control), for BBM and HDM-treated patients

Secondary endpoints

- Depth of best response (stable disease (SD), partial response (PR), very good partial response (VGPR), complete remission (CR), stringent complete remission (sCR)) after ASCT2
- Overall survival at 2 and 3 years after ASCT2
- Treatment related mortality at ASCT2
- Duration of neutropenia (ANC < 0,5) at ASCT2
- Time until engraftment
- Duration of hospitalization after stem cell infusion at ASCT2
- All severe adverse events according to version 5.0 of National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) during hospitalization and until day +100 after ASCT2.

Exploratory subgroup analysis

Prespecified subgroups will include depth of best response prior to ASCT2, any specific maintenance therapies following ASCT2, patients receiving G-CSF following ASCT, and patients receiving daratumumab as a part of induction or maintenance therapy at ASCT2.

In addition, we plan an exploratory subgroup analysis of patients with high-risk cytogenetics including p53-abberrations and patients with early relapse after ASCT1 (less than 3 years), although missing data is expected to be high.

Data points

General

- Date of birth
- Gender
- Comorbidities (diagnosis)
- Date of diagnosis of multiple myeloma
- Stage of multiple myeloma according to International staging system (ISS)
- Type of multiple myeloma (type of M-protein, Bence-Jones, non-secretory)
- Date of stem cell harvest
- Stem cell yield
- Prior myeloma-treatment (including agents)
    - Agents used in induction therapy for ASCT1 and ASCT2
    - Agents used in maintenance therapy after ASCT1 and ASCT2
    - Prior use of bortezomib and bendamustine
- Genetic abberations (including FISH) associated with multiple myeloma (exploratory data point)

    - Standard or high risk
    - Status of p53 or del(17p)
- Date of last follow-up

ASCT1 data

- Date of ASCT1
- Dose of stem cells given ASCT1
- Depth of response at ASCT1
- Best response after ASCT1
- Dose of melphalan in ASCT1

ASCT2 data

- Date of start of first relapse therapy prior to ASCT2
- Date of ASCT2
- Eastern Cooperative Oncology Group (ECOG) performance status at ASCT2
- Renal function (creatinine clearance) and hepatic function at ASCT2
- Dose of stem cells given ASCT2
- Depth of response at ASCT2
- Time to engraftment
- Duration of neutropenia (days)
- Days until total platelet count over 20 $x10^9$ without transfusions
- Frequency and grade of febrile neutropenia
- Duration of intravenous antibiotic therapy
- Need of parenteral nutrition
- Positive bacterial culture
- Confirmed viral infections/reactivations
- Confirmed fungal infections
- Duration of hospitalization after stem cell infusion
- Use of G-CSF including day(s)

Outcome

- Time to next treatment after ASCT1 and ASCT2
- Time to progression
- Best response before ASCT1 and ASCT2
- Best response after ASCT1 and ASCT2
- Date of start of relapse therapy after ASCT2

Safety

- Treatment related mortality
- Mortality incl date and cause
- Need for intensive care after ASCT2 including reason
- Frequency of serious adverse events (CTCAE grade 3 or higher)

Definitions

Engraftment
Absolute neutrophil count of 0.5 x 10^9/L or higher and total platelet count of 20 x 10^9/L and rising, without transfusion of thrombocytes.

Multiple myeloma, diagnosis
According to the International Myeloma Working Group (IMWG), clonal bone marrow plasma cells >10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following features and myeloma-defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
- Hypercalcemia: serum calcium >0.25 mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177mol/L (>2mg/dL)
- Anemia: hemoglobin value of >20g/L below the lowest limit of normal, or a hemoglobin value <100g/L
- Bone lesions: one or more osteolytic lesion on skeletal radiography, CT, or PET/CT. If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement
- 60% or greater clonal plasma cells on bone marrow examination
- Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100mg/L (a patient's involved free light chain either kappa or lambda is the one that is above the normal reference range; the uninvolved free light chain is the one that is typically in, or below, the normal range)
- More than one focal lesion on MRI that is at least 5mm or greater in size.

Progression free survival
The length of time between ASCT until the earlier of the date at which criteria for progressive disease (below) were met or the date of death.

Progressive disease
According to the international myeloma working group, progressive disease is defined as an increase of > 25% from lowest response value in any one or more of the following:

- Serum M-component and/or (the absolute increase must be > 0.5 g/dL). For progressive disease, serum M-component increases of >1 gm/dL are sufficient to define relapse if starting M-component is >5 g/dL.
- Urine M-component and/or (the absolute increase must be > 200 mg/24 h)
- Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL
- Bone marrow plasma cell percentage; the absolute percentage must be > 10%7
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Relapse
According to the international myeloma working group, clinical relapse requires one or more of:

- Development of new soft tissue plasmacytomas or bone lesions

- Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
- Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L]
- Decrease in haemoglobin of > 2 g/dL [1.25 mmol/L]
- Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]

Relapse from complete remission include any one or more of the following:

- Reappearance of serum or urine M-protein by immunofixation or electrophoresis
- Development of > 5% plasma cells in the bone marrow
- Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

Response definitions
According to the international myeloma working group;

- Stringent complete remission (sCR)
  CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
- Complete remission (CR)
  Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow
- Very good partial remission (VGPR)
  Serum and urine M-protein detectable by immunofixation but not on electrophoresis or > 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
- Partial remission (PR)
  - 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to < 200 mg/24 h
  - If the serum and urine M-protein are unmeasurable,5 a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
  - If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30%
  - In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required
- Stable disease
  Not meeting criteria for CR, VGPR, PR, or progressive disease

Time to next treatment (TNT)
The interval from ASCT to initiation of the next line of therapy, excluding any protocol-based maintenance therapy.

Treatment related mortality (TRM)
Death due to any transplantation-related cause other than disease progression.

Statistical analysis

Data will be summarized using frequencies for categorical variables, medians (range, interquartile range) for discrete variables and means (±SD) for continuous variables. To determine statistically significant differences between two groups, the Mann Whitney test will be used. To determine statistically significant differences between proportions, Fisher's exact test will be used. To determine statistically significant differences between

two time points, the Wilcoxon signed rank test will be used. Survival will be estimated using Kaplan-Meier plots (95%CI). A two-tailed p value <0.05 will be considered statistically significant. A linear multivariable regression analysis will be performed to estimate the effect of the most important confounder variables; depth of best response prior to ASCT2, use of daratumumab in induction therapy prior to ASCT2 and the use of maintenance therapy efter ASCT2.

Ethical committee approval

Approval from the Swedish Ethical Review Authority is a prerequisite to start the study.

All patients have provided written consent to allow their data to be reported to the European Society for Blood and Marrow Transplantation registry (EBMT).

Data management

Description of data

Data will be retrospectively collected and no new data points will be created for this study. The study will collect sensitive health care data, including data on diagnosis and mortality for the study subjects. The data points are described in this study protocol.

Storage and backup

All data will be pseudonymised and stored in an electronic case report file (eCRF) on a secure server at the entity responsible for the research. For backup, a password-locked mobile memory drive will contain the data in the same format. No online storage servers will be used. All communication with study data will be done with password-locked files and adhere to current GDPR rules. In any case of data analysis by an external partners, a data access agreement will need to be in place before such realization.

Legal and ethical aspects

The data in this study will only be shared with the investigators, principal investigator and scientific supervisor during the course of the study. All analysis of study data, including by the study investigators, will be performed on pseudonymised data.

Accessibility and long-term storage

The eCRF will be in Excel-format to ensure interoperability and reusability of the data. See section on data sharing below. Long-term storage will be done according to current GDPR rules, that is on a secure server belonging to the entity responsible for the research including back-up on a password-locked mobile memory drive stored in a safe (locked) place.

Data sharing

The study protocol will be registered at ClinicalTrials.gov before start of the study.

Individual participant data that underlie the results reported in this article, (text, tables, figures and appendices), will be available together with the study protocol after de-identification beginning 9 months and ending 5 years following article publication to researchers who provide a methodologically sound proposal. To gain access, data requestors will need to sign a data access agreement.

Work plan

Q2 2023 Application for ethical committee

Q3 2023	Start of data collection
Q3 2024	Start of data analysis
Q4 2024	Completion of final data analysis.
Q2 2025	Final report

Importance

As multiple myeloma is a chronic malignancy requiring long and recurrent periods of treatment, much value depends on the periods of suppressed disease activity following the first lines of treatment. This study aims to investigate whether or not conditioning with bortezomib-bendamustine-melphalan can extend the disease free period following ASCT for patients with multiple myeloma elegible for a second autologous hematopoietic stem cell transplantation without compromising safety. As there has been a fast development of new effective drugs as well as new indications for older drugs for multiple myeloma there is a clear rationale to investigate their role and combinations in the ASCT-setting. As the research question is directly clinical, this study could potentially change the protocol for ASCT in multiple myeloma patients.

References

1. Harousseau JL, Moreau P. Autologous hematopoietic stem-cell transplantation for multiple myeloma. The New England journal of medicine. 2009;360(25):2645-54.
2. McElwain TJ, Powles RL. High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. Lancet (London, England). 1983;2(8354):822-4.
3. Barlogie B, Hall R, Zander A, Dicke K, Alexanian R. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. Blood. 1986;67(5):1298-301.
4. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. The New England journal of medicine. 2017;376(14):1311-20.
5. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. The Lancet Haematology. 2020;7(6):e456-e68.
6. Al Hamed R, Bazarbachi AH, Malard F, Harousseau JL, Mohty M. Current status of autologous stem cell transplantation for multiple myeloma. Blood cancer journal. 2019;9(4):44.
7. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. The New England journal of medicine. 2008;359(9):906-17.
8. Leoni LM, Bailey B, Reifert J, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. Clinical cancer research : an official journal of the American Association for Cancer Research. 2008;14(1):309-17.
9. Pönisch W, Mitrou PS, Merkle K, et al. Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone--a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). Journal of cancer research and clinical oncology. 2006;132(4):205-12.
10. Roussel M, Moreau P, Huynh A, et al. Bortezomib and high-dose melphalan as conditioning regimen before autologous stem cell transplantation in patients with de novo multiple myeloma: a phase 2 study of the Intergroupe Francophone du Myelome (IFM). Blood. 2010;115(1):32-7.
11. Roussel M, Hebraud B, Lauwers-Cances V, et al. Bortezomib and High-Dose Melphalan Vs. High-Dose Melphalan As Conditioning Regimen before Autologous Stem Cell Transplantation in De Novo Multiple Myeloma Patients: A Phase 3 Study of the Intergroupe Francophone Du Myelome (IFM 2014-02). Blood. 2017;130(Supplement 1):398-.
12. Gimsing P, Hjertner Ø, Abildgaard N, et al. Salvage bortezomib-dexamethasone and high-dose melphalan (HDM) and autologous stem cell support (ASCT) in myeloma patients at first relapse after HDM with ASCT. A phase-2 trial. Bone marrow transplantation. 2015;50(10):1306-11.
13. Mark TM, Reid W, Niesvizky R, et al. A phase 1 study of bendamustine and melphalan conditioning for autologous stem cell transplantation in multiple myeloma. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2013;19(5):831-7.
14. Martino M, Tripepi G, Messina G, et al. A phase II, single-arm, prospective study of bendamustine plus melphalan conditioning for second autologous stem cell transplantation in de novo multiple myeloma patients through a tandem transplant strategy. Bone marrow transplantation. 2016;51(9):1197-203.
15. Farag S, Jeker B, Bacher U, et al. Dose-intensified bendamustine and melphalan (BenMel) conditioning before second autologous transplantation in myeloma patients. Hematological oncology. 2018;36(4):671-8.
16. Gomez-Arteaga A, Mark TM, Guarneri D, et al. High-dose bendamustine and melphalan conditioning for autologous stem cell transplantation for patients with multiple myeloma. Bone marrow transplantation. 2019;54(12):2027-38.
17. Sweden S. Population statistics - Quarter 4, 2022: Statistics Sweden; 2023 [Available from: https://www.scb.se/en/finding-statistics/statistics-by-subject-area/population/population-composition/population-statistics/pong/tables-and-graphs/population-statistics---month-quarter-half-year/population-statistics---quarter-4-2022/.