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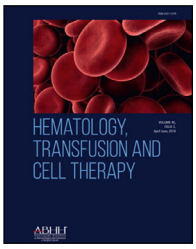

Special article

Guidelines on the diagnosis and management of multiple myeloma treatment: Associação Brasileira de Hematologia e Hemoterapia e Terapia Celular Project guidelines: Associação Médica Brasileira – 2022. Part I

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ARTICLE INFO

Article history:
Received 17 June 2022
Accepted 29 June 2022
Available online 20 July 2022

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize producers to assist the reasoning and decision-making of doctors. The information provided through this project must be assessed and criticized by the physician responsible for the conduct that

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https://doi.org/10.1016/j.htct.2022.06.003

will be adopted, depending on each patient's conditions and clinical status.

The data contained in the following articles were prepared by and are recommended by the Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular (ABHH). Even so, all possible medical approaches should be evaluated by the physician responsible for treatment depending on patient's characteristics and clinical status.

Questions

1. What is the age limit for autologous stem cell transplantation?
2. What is the best combination for the patient's initial treatment eligible for autologous stem cell transplantation: three or four drugs from different therapeutic classes?
3. Is high-dosage therapy with melphalan 200mg/m^2 superior to busulfan and melphalan?
4. Would two transplants be better than one transplant?
5. Is post-transplant consolidation indicated for all patients?
6. Is post-transplant maintenance indicated for all patients?
7. Is there a role for allogeneic transplantation?

Introduction

The following Guideline updates the first publication issued in 2012 by the Multiple Myeloma Committee of the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy (ABHH).[1]

Methods

This Guideline is backed up by a systematic review that seeks to address the questions raised by the panel of experts.

The evidence search will occur in the virtual scientific information databases: Medline and EMBASE.

The following data were extracted from the studies: author's name and year of publication, study population, intervention and comparison methods, the absolute number of events, follow-up time.

The risks of bias of the included randomized controlled trials were analyzed according to the following criteria: focal issue, randomization, blinded allocation, double-blinding, losses less than 20%, intention-to-treat analysis, prognostic characteristics, presence of the outcome that matters, time to the outcome, method of outcome measurement, sample size calculation, early termination, and JADAD (scale ranging from 0 to 5 points, which takes randomization, double-blinding, and losses into account).

The metrics used to express benefit and harm varied according to the outcomes and were expressed by continuous variables (mean and standard deviation) or categorical variables (absolute number of events). In continuous measures, the results will be differences in means and standard deviation, and in categorical measures, they will be differences in risks and numbers needed to treat or produce harm, considering the number of patients. The confidence level used was 95%.

The results of the included studies could be aggregated and meta-analyzed using RevMan 5.3 software.

In addition, the quality of evidence will be graded as high, moderate, low, or very low by the GRADE instrument, taking into consideration the risk of bias, the presence of inconsistency, imprecision, or indirect evidence in the meta-analysis of the outcomes, and the presence of publication bias.

PICO 1: What is the age limit for autologous stem cell transplantation?

Goal

This Guideline aims to identify the age limit for performing autologous stem cell transplantation, defining the benefits and harms for the analyzed ages.

Methods

This systematic review is based on the following clinical question, "What is the age limit for autologous stem cell transplantation in patients with Multiple Myeloma?"

The eligibility elements of the studies are:

1. Adult patients with a diagnosis of Multiple Myeloma;
2. Comparison between groups: elderly (more than 60 years) and non-elderly (less than 60 years);
3. Use of melphalan (100-200 mg/m^2) as a conditioning regimen ;
4. No time limit;
5. No language limit;
6. Full text available for Access;
7. Tandem autologous or allogeneic transplantation was excluded.

The search for the evidence was conducted in the Medline and EMBASE virtual scientific information databases using the following strategies:

Medline: (((((multiple myeloma) AND (transplantation OR transplant) AND autologous))))) AND (((((((incidence [MeSH: noexp] OR mortality[MeSH Terms] OR follow up studies [MeSH:noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word])))))) OR ((((prognos*[Title/Abstract] OR (first [Title/Abstract] AND episode [Title/Abstract]) OR cohort [Title/Abstract])))))) OR (((age OR aged OR elderly OR older OR "60 years" OR "65 years" OR "70 years" OR "75 years"))))).

EMBASE: ((multiple myeloma) AND (transplantation OR transplant) AND autologous) AND (age OR aged OR elderly OR older OR 60 years OR 65 years OR 70 years OR 75 years).

The studies yielded the following data: author's name and year of publication, study population, intervention and comparison methods, the absolute number of events, and follow-up time.

The bias analysis was performed using the Robins-I tool for non-randomized studies (in this case, cohort studies).

The measures used to express benefit and harm varied according to the outcomes and expressed through continuous variables (mean and standard deviation) or categorical variables (absolute number of events). In continuous measures, the results will be differences in means and standard deviation, and in categorical measures, they will be differences in risks and numbers needed to treat or produce harm, considering the number of patients. The confidence level used was 95%.

Results

The age limit for considering a patient eligible for autologous stem cell transplantation) (ASCT) for patients with Multiple Myeloma (MM) is a matter of controversy. In Brazil, an ordinance from the (SNT) Sistema Nacional de Transplantes (SNT) limits the procedure to patients up to 75 years old. In Europe, this limit is 65 years, and there is no pre-established limit in the USA.

Patients with MM (n = 13,884) who underwent ASCT were divided into two groups (elderly and non-elderly) in the methodological analysis recommended in this Guideline.

Regarding overall survival (OS) , comparing the non-elderly group with the elderly group after five years of median follow-up, we found a higher rate of OS in patients younger than 65 years (58.2% [95%CI, 54.2-62.1%]) when compared to those older than 65 years (42.6% [95%CI, 31.6-53.2%]).[2] It was also shown that after three years, there was a higher OS in the 18 to 59-year-old group (78% [95%CI, 76-79]) when compared to the patients aged 70 years and older (72% [95%CI, 67-76]).[3] When it comes to progression-free survival (PFS) , there was no significant difference between the elderly and non-elderly. Relapse-free mortality seems to be higher in the elderly than in non-elderly patients.[2-5]

Recommendations

ASCT may be indicated in older patients with a possible age limit of 75 years.The studies evaluated do not allow a clear conclusion about a chronological age limit due to a possible selection bias in the indication of ASCT in older patients, because of the inclusion in the studies of almost only patients without severe comorbidities and with better performance status. It should be noted that the increasing improvement of treatment outcomes in patients not eligible for ASCT points to a trend toward limiting this procedure to younger patients, age < to 65 years, with a more cautious indication for patients between 65 and 75 years.

PICO 2: What is the best combination for the patient's initial treatment eligible for autologous stem cell transplantation: three or four drugs from different therapeutic classes?

Goal

The present Guideline aims to determine which combination is best for the patient's initial treatment eligible for autologous stem cell transplantation (ASCT), defining the benefits and harms of each combination analyzed.

Methods

In support of this Guideline, this systematic review seeks to answer the following clinical question: “Which combination is best for the initial treatment of the transplant-eligible patient: with three or four drugs from different therapeutic classes?”

The study eligibility elements consist of:

1. Adult patients diagnosed with Multiple Myeloma (MM)
2. Eligible patients for autologous stem cell transplantation (ASCT)
3. Studies that perform the initial patient treatment (pre-transplant) by comparing three drugs from different therapeutic classes and four drugs from different therapeutic classes
4. Randomized Clinical Trials (RCT)
5. No time limit
6. No language limit
7. Full text available

The evidence search will be performed using the virtual scientific information databases Medline and EMBASE. The search strategies consist of:

Medline: (multiple myeloma) AND (Lenalidomide OR Thalidomide OR Cyclophosphamide OR Daratumumab) AND ((transplantation OR transplant) AND autologous)).

EMBASE: ('multiple myeloma'/exp OR 'multiple myeloma' OR (multiple AND ('myeloma'/exp OR myeloma))) AND ('daratumumab'/exp OR daratumumab) AND [embase]/lim AND ('transplantation'/exp OR transplantation OR 'transplant'/exp OR transplant) AND autologous.

Results

Patients with MM eligible for (ASCT) were allocated into two initial treatment groups (three or four drugs from different therapeutic classes) and analyzed for five central endpoints: response after induction, response after ASCT, OS, PFS, and toxicity.

The current recommended standard of care for the initial treatment of patients eligible for ASCT should include a proteasome inhibitor in combination with two or three other drugs from distinct classes. A single randomized trial showed an advantage in terms of depth of response (above "very good" partial remission) in favor of the combination of bortezomib, thalidomide, and dexamethasone (VTD) over bortezomib, cyclophosphamide, and dexamethasone (VCD).[6]

No randomized studies compare VTD and bortezomib, lenalidomide and dexamethasone (VRd). However, one study uses historical control from the PETHEMA Group that compared these two strategies. That study showed an advantage in depth of response and PFS , favoring six cycles of VRd compared to six VTD cycles. A higher incidence of peripheral neuropathy and discontinuation due to adverse events was observed in the VTD-treated group.[7,8]

Regarding the addition of a fourth drug to the regimen, a single randomized trial (Cassiopeia) showed an advantage in depth of response and PFS for the combination of daratumumab + VTD (DaraVTD)compared to VTD.[9] The

combinations of daratumumab + VRD or Isatuximab + VRD are still under clinical investigation.[10]

Recommendations

Initial treatment for patients eligible for ASCT should be with four to six induction cycles using a regimen containing three or four drugs from distinct therapeutic classes. The advised regimens are either DaraVTD (Grade IA) or VRd (Grade IIB). VTD (Grade IA) and VCD (Grade IIB) are alternatives if the preferred regimens are unavailable.

PICO 3: Does high-dose chemotherapy with melphalan 200mg/m2 outperform busulfan and melphalan?

Structured question

P: Patients with symptomatic MM with an indication for autologous stem cell transplantation

I: Melphalan 200 mg/m^2 (MEL 200)

C: Melphalan + Busulfan (BU + MEL)

O: Overall survival/progression-free survival/ response rate/ toxicity

Methods

This Guideline is an update responding to the same query drafted in 2012.

The eligibility criteria used were PICO elements and comparative studies; the period consulted started in 2013 to update the previous Guideline; No language limit; Abstracts or full-text papers. The selected studies will be annexed after the studies described within the 2012 Guideline text.

The search for the evidence was performed in Medline, EMBASE, CENTRAL, using the strategy: (multiple myeloma) AND (Busulfan) AND (melphalan). The manual and grey literature searches were also performed.

The data extracted from the selected studies were: author, year, study design, description of the population, intervention, and comparison, follow-up time, as well as the outcomes overall survival, progression-free survival, response rate, mortality, and toxicity.

Outcomes will be expressed as the number of events in each group, the difference in risk between the compared treatment modalities, and numbers needed to treat (NNT) or to harm (NNH) whenever the difference is significant (95% confidence level). The results will not be meta-analyzed.

Results

The use of melphalan 200 mg/m^2 (MEL 200) is considered the standard as high-dose therapy prior to ASCT . Few studies have tested a new approach in this setting.

Comparing two conditioning regimens, Mel 200 versus melphalan 100 mg/m^2 associated with busulfan (16 mg/kg) showed a 10% increase in overall response rate (ORR) and a higher PFS at five years, although the OS is similar.[11]

In another study, a comparison of busulfan (12 mg/kg) associated with melphalan 140 mg/m^2 versus Mel 200 showed similar results regarding the length of hospitalization and graft engraftment. Mel 200 reduced mortality by 4.9%, despite a lower PFS .[12]

The use of melphalan associated with venous busulfan has been tested in randomized studies. In one study, patients up to 70 years old were treated with either BuMEL (104 patients) or Mel 200 (298 patients). At a median follow-up time of 22.6 months and 20.2 months, respectively, the 3-year OS was 91% in the BuMEL group and 89% in the Mel 200 group. The median PFS was 64.7 months with BuMEL and 43.5 months with Mel 200. Grade 3-4 non-hematologic toxicity was higher in the intervention group (BuMEL), 84% and 33%, respectively.[13]

In another randomized study, patients up to 65 years old were treated with BuMEL (51 patients) or with Mel 200 (102 patients) at a follow-up time of 50 and 63 months, respectively. The median OS was not different between the two groups (BuMEL 65.5 months and 63 months in the Mel 200 group). The PFS was 23% and 17%, respectively. There were 2 cases of treatment-related mortality (TRM)) observed in both groups.[14] The study was updated with a 5-year follow-up, and there was no significant difference in median OS between the two groups; it was 65.7 months in the BuMEL group and 65.1 months in the Mel 200 group. PFS at five years was 31% and 22.5%, respectively, and there was an increase in PFS of 8.5% with the use of BuMEL compared to Mel 200.[15]

Recommendations

Melphalan 200 mg/m^2 is the standard regimen for high-dose therapy (Grade 1A) before ASCT . There is controversy in comparing the results obtained with conditioning using BuMEL or Mel 200. There seems to be an advantage in PFS in the BuMEL combination but no advantage in OS and higher toxicity.

PICO 4: Would two transplants be better than one transplant?

Structured question

P: Patients with symptomatic MM with an indication for autologous stem cell transplantation undergoing high-dose chemotherapy

I: One transplant followed by

C: Two transplants

O: Overall survival / progression-free survival / response rate / toxicity

Methods

This Guideline is an update of the Guideline answering the same question developed in 2012.[1]

The eligibility criteria used were: PICO elements and comparative studies. The period consulted was from 2013 to update the previous Guideline, with no limit of language, abstracts, or full texts. The selected studies will be attached in the sequence of the studies described in the text of the 2012 Guideline.

The search for the evidence was performed in Medline, EMBASE, CENTRAL, using the strategy: ((multiple myeloma) AND (transplantation OR transplant) AND (autologous OR tandem)). The manual and grey searches were also performed.

The data extracted from the selected studies were: author, year, study design, description of the population, intervention,

and comparison, follow-up time, as well as the outcomes overall survival, progression-free survival, response rate, mortality, and toxicity.

The outcomes will be expressed as the number of events in each group, the difference in risk between the compared treatment modalities, and numbers needed to treat (NNT) or to harm (NNH) whenever the difference is significant (95% confidence level). The results will not be meta-analyzed.

Results

There is considerable controversy regarding the potential role played by the consolidation using a 2nd ASCT . Retrospective and randomized studies performed between 1990 and 2010 reported contradictory results regarding that strategy.[16-18]

In a more recent randomized trial (STaMINA) , 758 patients who received induction therapy up to twelve cycles were selected to receive Mel 200, followed by ASCT . Patients were randomized into three groups. The first group received an additional Mel 200 followed by maintenance with lenalidomide. The second group received consolidation with four cycles of VRd and maintenance with lenalidomide. The third group received only maintenance with lenalidomide. The response rates, PFS , OS in addition to toxicity, were similar among the three study groups.[19]

In another study, patients with MM were randomized into two groups to receive high-dose melphalan therapy followed by one or two ASCTs . After a median follow-up of 11 years, no inferiority was demonstrated for the group receiving a transplant in the endpoints of PFS at two years (p = 0.53) and in OS (p = 0.33) after intention-to-treat analysis. OS after the first relapse was significantly reduced in the double transplant group (p = 0.04).[20]

The use of a planned second ASCT as consolidation was also tested in the EMN02 / HO95 study in centers with a dual ASCT policy. Patients were randomized to receive bortezomib, melphalan, and prednisone (VMP) , single ASCT (ASCT -1), or double ASCT (ASCT-2) administered 2-3 months apart. Patients who received ASCT -2 had prolonged PFS compared to those who received ASCT 1. PFS probability at three years was 53.5% for ASCT 2 versus 44.9% for the ASCT -1 Group (P = 0.036). That represented a 26% reduction in the risk of progression or death, favoring the ASCT -2 group. The greatest benefit was seen in patients with high-risk cytogenetics (mPFS: 46 and 26.7 months for ASCT -2 and ASCT -1, respectively; HR = 0.59; P = 0.062). Also, the OS at first randomization was significantly prolonged in patients receiving ASCT -2 compared with ASCT-1 (89% versus 82%; HR = 0.52; P = 0.011); this benefit was also demonstrated in patients with R-ISS II + III (HR = 0.48; P = 0.013) and with high cytogenetic risk (HR = 0.52; P = 0.042).[21]

Recommendations

Controversial exists as to whether the double transplantation in patients with MM increases OS,PFS and response rate compared to single ASCT . For the subgroup of patients with high cytogenetic risk (t (4;14), t (14;16), del17 p), there is a potential benefit to double ASCT in terms of depth of response PFS and OS . (Grade 1A).

PICO 5: Is post-transplant consolidation indicated for all patients?

Methods

Structured questions

P: patients with symptomatic Multiple Myeloma, indicated for autologous stem cell transplantation

I: post-transplant consolidation

C: bortezomib + thalidomide + dexamethasone / bortezomib + cyclophosphamide + dexamethasone / bortezomib + lenalidomide + dexamethasone

O: overall survival / progression-free survival / response rate / adverse events

Eligibility criteria

Patient with symptomatic MM with the indication for autologous stem cell transplantation (ASCT) , undergoing post-transplant consolidation with one of the following regimens: bortezomib + lenalidomide + dexamethasone (VRd), bortezomib + thalidomide + dexamethasone (VTD), bortezomib + thalidomide + prednisone (VTP), bortezomib + dexamethasone (VD), thalidomide + dexamethasone (TD), VRd + lenalidomide (Len), thalidomide + prednisone (TP), bortezomib + dexamethasone (VD), prednisone (P), with analysis of overall survival (SG) or progression-free survival (PFS) or response rate (RR) or adverse events (AE); Study design: Randomized clinical trials (RCTs) or cohort studies; no limitation on query period or language; full text or abstract with data.

Selection of papers retrieved from virtual information bases

Articles identified in the search evaluated by title and abstract: 289

Selected papers: 25

Full texts accessed for eligibility: 25

Studies included in the qualitative synthesis: 11

Reasons for exclusion (14): Case series (7); Study protocol (1); Review (1); Post-hoc analysis (1); Maintenance (1); Phase II clinical trial (1); Only one arm of BMT (1); No consolidation study (1).

Evidence search

The scientific databases consulted were Medline, EMBASE, CENTRAL Cochrane.

Evidence selection

Two independent reviewers performed the evidence selection. Initially, the title and abstract were observed. The papers that met the eligibility criteria had their full texts analyzed.

Data extraction

The data extracted included: name of the author, year of publication, characteristics of the population, interventions, and outcomes [overall survival (OS) and progression-free survival (PFS), response rate (RR) and toxicity], and follow-up time. Outcome expression measures were the absolute number of outcomes and population number, absolute risk, risk difference, 95% confidence level. When there was the expression in the mean, the difference of means with standard deviation was calculated.

Risk of bias and quality of evidence

The following items were considered in the risk of study bias: randomization, blinded allocation, double-blinding, evaluator blinding, losses, outcomes, prognostic characteristics, intention-to-treat (ITT) analysis, sample size, early termination, and can be classified as not severe, severe, or very severe.

Analysis and expression of results

As possible, the outcomes of studies with common characteristics and outcomes were grouped for the eventual development of meta-analysis. If grouping and meta-analysis are not possible, the results will be expressed and discussed separately. In the different studies synthesized, the VTD, VCD, and VRd arms were considered, compared to the results of different combinations called controls according to the structured question. The controls for each analysis will be explained in the results.

Results

One of the possible strategies to improve the response and survival of patients undergoing ASCT would be to use a consolidation with two to four cycles of combination therapy. However, the actual role of this strategy remains controversial.

Included in this systematic review were 11 randomized clinical trials and 01 cohort study, totaling 4,766 patients. The inclusion criteria adopted by these studies were restricted to patients between 18 and 65 years of age, with symptomatic MM and eligible for ASCT . Only one study evaluated post-transplant consolidation versus no consolidation, while the other studies evaluated only which regimen was best during the consolidation phase.

In two randomized clinical trials (RCT)[22-24] involving 795 patients, the effects of consolidation with VTD versus TD were evaluated. Summing up their results for the outcomes evaluated, we have OS : 88% vs. 86%, PFS : 65% vs. 53% at 36 months, RR: 59% vs. 43 %, respectively. As for adverse events, a rate of 38% vs. 24% was reported for any grade 3 or 4 events, respectively.

In one study patients receiving three induction cycles of bortezomib-cyclophosphamide-dexamethasone (VCD) followed by ASCT were randomized (1: 1) to consolidation with TP (thalidomide 100 mg / d for ≤12 months / until disease progression; prednisolone 50 mg on alternate days indefinitely / until disease progression; n = 100) or VTP (subcutaneous bortezomib 1.3 mg/m^2 every two weeks for 32 weeks, plus TP; n = 103). The difference in CR + VGPR rate (after ≤12 months of consolidation therapy) was not reached (85.7% versus 77.1%; rate difference 8.6%; 95% confidence interval -2.3% -19.5%; p = 0.122). Secondary efficacy outcomes were similar between treatment arms. The addition of bortezomib to TP consolidation was associated with limited additional toxicity but did not significantly improve efficacy over TP.[25]

Another study evaluated VRD versus RD consolidation therapy in patients with a full induction regimen with dexamethasone. Forty-eight patients were divided into two groups according to the proposed consolidation therapy. The OS rate was 69 months vs. 60 months (HR 0.77 - 95% CI: 0.35-1.70), PFS: 20 months vs. 18 months (HR 0.96 - 95% CI: 0.53-1.75) and RR: 81% vs. 63% (OR 2.6 - 95% CI: 0.52, 13.0), respectively. Adverse effects with grade ≥3 showed rates of 65% vs. 64%, respectively.[26]

The only cohort study added to this systematic review investigated the efficacy and safety of consolidation therapy with VTD in patients who underwent induction and VTD followed by ASCT, compared to patients who did not undergo consolidation therapy. 217 patients were included, with 121 patients undergoing the proposed intervention (VTD + transplantation + VTD) and 96 patients belonging to the comparison arm (VTD + transplantation). The results showed OS rates: 96% vs. 91% and TR rates: 52% vs. 30% (p= 0.001), respectively.[27]

As previously cited, the STaMINA study evaluated the role of consolidation with a double ASCT or four cycles of VRd or maintenance alone with lenalidomide. This study showed no differences in depth of response, PFS , and OS between the three patient groups.[19]

Recommendations

The role of consolidation after ASCT remains controversial, and it is not possible to state what the differences in benefit or harm were with consolidation therapy compared to no consolidation.

PICO 6: Is post-transplant maintenance indicated for all patients?

Method

Structured question

P: patients with symptomatic Multiple Myeloma with the indication for autologous c stem cell transplantation

I: post-transplant maintenance

C: lenalidomide / thalidomide / dexamethasone / ixazomib / daratumumab

O: overall survival / progression-free survival / response rate / adverse events

Eligibility criteria

Patient with symptomatic Multiple Myeloma (MM) indicated for autologous stem cell transplantation (ASCT), undergoing post-transplant maintenance with one of the following regimens: lenalidomide (Lena), thalidomide (Tal), dexamethasone (Dexa), ixazomib (Ixa), and daratumumab (Dara), with analysis of overall survival (OS) or progression-free survival (PFS) or response rate (RR) or adverse events (AE); Study design: randomized clinical trials (RCTs) or cohort studies; no limitation of consultation period or language; full text or abstract with data.

Selection of the papers retrieved from the virtual information bases

Articles identified in the search evaluated by title and abstract: 1,231

Articles selected: 28

Full texts accessed for eligibility: 28

Studies included in the qualitative synthesis: 16

Reasons for exclusion (12): Case series (2); Intermediate outcome (1); Review (2); Does not assess maintenance (3); Unable to extract results (4).

Evidence search

The following scientific databases were searched: Medline, EMBASE, CENTRAL Cochrane.

Evidence selection

The evidence selection was performed by two independent reviewers, initially by title and abstract, and the papers that met the eligibility criteria their full texts were accessed.

Data extraction

The data extracted were: author's name, year of publication, characteristics of the population, interventions, and outcomes [overall survival (OS) and progression-free survival (PFS), response rate (RR), and adverse effects (AE)], and follow-up time. The outcome expression measures were the absolute number of outcomes and population number, absolute risk, risk difference, 95% confidence level. When there was an expression in the mean, the difference of means with standard deviation was calculated.

Risk of bias and quality of evidence

The following items were considered in the risk of bias in the studies: randomization, blinded allocation, double-blinding, observer blinding, losses, outcomes, prognostic characteristics, intention-to-treat (ITT) analysis, sample size, early termination, and can be classified as not severe, severe, or very severe.

Analysis and expression of results

Whenever possible, the results of studies with common characteristics and outcomes were grouped for possible development of meta-analysis. If grouping and meta-analysis are not possible, the results will be expressed and discussed separately. In the different studies synthesized, the Lena, Tal, Dexa, Ixa, and Dara arms were considered, compared to the results of different combinations called controls according to the structured question. The controls for each analysis will be explained in the results.

Results

In addition to consolidation, another strategy widely used to increase the depth of response and prolong the PFS and OS of patients after ASCT is the maintenance for a fixed period or until disease progression.

In the systematic review for this Guideline, ten randomized clinical trials (RCTs and six observational studies were included, totaling 7,288 patients. Of the twenty studies included, twelve did not use drug therapy in the comparison arm, while the remaining studies evaluated only which regimen was best for the maintenance phase.

The development of meta-analysis was possible with the grouping of seven studies,[28-34] which compared patients undergoing maintenance therapy with lenalidomide (Lena) versus no maintenance or placebo for the possible outcomes adopted. In this meta-analysis, lenalidomide showed an advantage in terms of PFS but not in terms of OS and response rate. A higher rate of adverse events (26%) was identified in the lenalidomide-treated group compared to the no-maintenance group.

A meta-analysis published in 2019, including over 1,200 patients from three RCTs, with a median follow-up of 79.5 months, showed that maintenance with lenalidomide showed an advantage in PFS (52.8 versus 23.5 months) and OS benefit over placebo. Grade 3 and 4 adverse events, including second malignancy, were more frequently observed in the group of patients receiving lenalidomide. In this study, there was no benefit from the use of lenalidomide for patients with ISS-III disease or high-risk cytogenetics.[35]

However, considering this high cytogenetic risk patient population, the Medical Research Council (MRC) Myeloma-XI RCT showed an advantage in terms of 3-year OS for the lenalidomide group compared to placebo (75% X 64%).[36]

Bortezomib was evaluated compared to thalidomide in an RCT involving 499 patients, showing an advantage in PFS (28 months vs. 35 months (p= 0.002)). This advantage was most evident for the group of patients with high-risk cytogenetics (t 4;14 and del 17p). However, differences in study design regarding induction treatment do not allow a definitive conclusion.[37]

Only one RCT used ixazomib in its evaluation compared to a placebo in 656 patients. The results showed an PFS of 26.5 months vs. 21.3 months (p= 0.0023), a RR of 15% vs. 21%, and an AE of 78% vs. 58% for any event.[38]

Recommendations

Maintenance with lenalidomide should be considered the standard for all patients with MM post-ASCT (I, A).

For the other agents, it is impossible to state the differences in benefit or harm with maintenance therapy compared to no maintenance, or, when maintenance therapy is indicated, which is the best therapeutic regimen to adopt.

Maintenance with bortezomib associated with lenalidomide may be considered for patients with high-risk disease (II, B).

PICO 7: Is there a role for allogeneic transplantation?

In this update, 3,700 papers were retrieved by searching the scientific databases. After the initial reading by title and abstract, the full texts, and eliminating duplicates, two papers and two meta-analyses meeting the eligibility criteria were selected to support the recommendations.

When comparing autologous with allogeneic transplantation in patients with MM, there is no evidence of a difference in RR ,OS and PFS were higher in patients undergoing allogeneic transplantation. Transplant-related toxicity and mortality are also higher in allogeneic transplants.[39,40]

Several studies have evaluated the strategy in combining an ASCT followed by reduced-intensity allogeneic BMT (tandem auto/alo) and comparing it with the double ASCT strategy (tandem auto/auto). In two meta-analyses, it was shown that despite the superiority in terms of CR favoring tandem auto/alo, there was no increase in OS compared to tandem auto/auto , possibly due to the high mortality rate related to the procedure.[41,42]

Recommendations

The quality of the evidence is low. In patients with MM eligible for ASCT , allogeneic transplantation associated or not with autologous transplantation determines more prolonged

PFS and minor relapse. However, the toxicity and mortality related to the procedure exclude the recommendation of allogeneic transplantation from the routine treatment of MM .

Conflicts of interest

I certify that (1) the study submitted has not received any financial support from pharmaceutical industry or other commercial source except those described below, and (2) neither I, nor any first-degree relative possess any financial interest in the subject approached in the manuscript.

Ethical statement

The author(s) state(s) that this research was conducted in accordance with the Helsinki Declaration as revised in 2008. In all studies involving animals, the author(s) followed the guidelines for the use and care of laboratory animals of the author's institution or the National Research Council or any national law pertaining to care of animals in research.

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