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on multiple myeloma | rare diseases

COVID-19 vaccination in patients with multiple myeloma:
a consensus of the European Myeloma Network

The Lancet Haematology, 2021 December; 8(12):e934–46

Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE):
a randomised, open-label, phase 2 trial

The Lancet Oncology, 2021 December; 22(12):1705–20

Safety and effectiveness of weekly carfilzomib, lenalidomide, dexamethasone, and daratumumab combination therapy for patients with newly diagnosed multiple myeloma:
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Consolidation and maintenance in newly diagnosed multiple myeloma

Journal of Clinical Oncology, 2021 November 10; 39(32):3613–22

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JAMA Oncology, 2021 November 1; 7(11):1678–85

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Blood Cancer Journal, 2021 December 2; 11(12):192

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COVID-19 VACCINATION IN PATIENTS WITH MULTIPLE MYELOMA:

A CONSENSUS OF THE EUROPEAN MYELOMA NETWORK

The Lancet Haematology, 2021 December; 8(12):e934–46

AUTHORS: Ludwig H, Sonneveld P, Facon T, et al.
CENTRE FOR CORRESPONDENCE: Wilhelminen Cancer Research Institute, First Department of Medicine, Center for Oncology, Hematology, and Palliative Care, Vienna, Austria

BACKGROUND & AIM: People with multiple myeloma (MM) may develop myeloma-induced or treatment-induced immunosuppression, which puts them at an increased risk of infection, including infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). People with MM and SARS-CoV-2 infection generally have prolonged illness and an increased risk of death. It is therefore important that people with MM are protected against the development of coronavirus disease 2019 (COVID-19). The European Multiple Myeloma Network evaluated the data available on SARS-CoV-2 infection in people with MM and developed consensus recommendations on vaccination to prevent COVID-19 in these individuals.

TYPE OF ARTICLE: Consensus recommendations.

FINDINGS: It is recommended that all people with MM and their families should receive a COVID-19 vaccine. If possible, people with MM should be vaccinated during periods when their disease is well controlled and when they are not receiving antimyeloma therapy. The vaccine should be administered before stem-cell collection or more than 3 months after autologous haematopoietic stem-cell transplantation. Those with a history of COVID-19 should also be vaccinated.

Available data suggest that some people with MM have a suboptimal immune response against SARS-CoV-2 following vaccination, which means they may remain unprotected. One group that is particularly at risk of a poor vaccine response comprises those with uncontrolled MM, although vaccination should still be considered on an individual basis. Other risk factors include older age, immunoparesis, a large number of lines of therapy and receipt of certain MM treatments (e.g. anti-CD38 antibodies and B-cell maturation antigen-directed therapy).

Evaluation of the immune response to vaccination is generally not recommended by official organizations; however, it might make it possible to identify people with MM who have a low or no response to vaccination. As a result, decisions could be made about subsequent clinical management, such as administering a third dose of vaccine or temporary treatment discontinuation.

Individuals with an inadequate immune response will benefit from 'ring' vaccination, which should include their family and household members, close social contacts and any healthcare personnel involved in their care. These individuals should also adhere to general measures for reducing the risk of infection. For immunosuppressed individuals who are exposed to the virus or who contract COVID-19, consideration can be given to administering protective monoclonal antibodies (e.g. casirivimab and imdevimab). Convalescent plasma may also be an option for prophylaxis against COVID-19.

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CARFILZOMIB WITH CYCLOPHOSPHAMIDE AND DEXAMETHASONE OR LENALIDOMIDE AND DEXAMETHASONE PLUS AUTOLOGOUS TRANSPLANTATION OR CARFILZOMIB PLUS LENALIDOMIDE AND DEXAMETHASONE, FOLLOWED BY MAINTENANCE WITH CARFILZOMIB PLUS LENALIDOMIDE OR LENALIDOMIDE ALONE FOR PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (FORTE):

A RANDOMISED, OPEN-LABEL, PHASE 2 TRIAL

The Lancet Oncology, 2021 December; 22(12):1705–20

AUTHORS: Gay F, Musto P, Rota-Scalabrini D, et al.
CENTRE FOR CORRESPONDENCE: SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Division of Haematology, University of Torino, Azienda Ospedaliero–Universitaria Città della Salute e della Scienza di Torino, Turin, Italy

BACKGROUND & AIM: Bortezomib is used as part of the standard-of-care treatment for young, fit people with newly diagnosed multiple myeloma (NDMM), but is associated with neurotoxic adverse events. In comparison, carfilzomib is associated with negligible neurological toxicity. The aim of this study was to compare the efficacy of different carfilzomib-based regimens in people with NDMM.

STUDY DESIGN: Randomized, open-label, phase 2 clinical trial.

ENDPOINTS: Primary: proportion of participants with at least a very good partial response after induction; progression-free survival (PFS) with maintenance treatment. Key secondary: stringent complete response rate; PFS after induction.

METHOD: Transplant-eligible individuals younger than 65 years with NDMM were randomized to receive: (1) induction with four cycles of carfilzomib, lenalidomide and dexamethasone (KRd), intensification with high-dose melphalan plus autologous stem-cell transplantation (ASCT) and consolidation with four cycles of KRd (KRd + ASCT; *n*=158); (2) 12 cycles of KRd (KRd12; *n*=157); or (3) induction with four cycles with carfilzomib, cyclophosphamide and dexamethasone (KCd), intensification with high-dose melphalan plus ASCT, and consolidation with four cycles of KCd (KCd + ASCT; *n*=159). All participants were subsequently randomized to maintenance with carfilzomib plus lenalidomide (*n*=178) or lenalidomide alone (*n*=178).

RESULTS: The median duration of follow-up from the first and second randomizations was 50.9 months (interquartile range 45.7–55.3 months) and 37.3 months (IQR 32.9–41.9 months), respectively. Overall, 222 of 315 participants (70%) given KRd and 84 (53%) of those given KCd had at least a very good partial response after induction (odds ratio 2.14, 95% confidence interval 1.44–3.19; *p*=0.0002). The stringent complete response rate was 32% with KCd + ASCT, compared with 46% with KRd + ASCT (OR 1.77, 95% CI 1.12–2.81; *p*=0.014) and 44% with KRd12 (OR 1.66, 95% CI 1.05–2.63; *p*=0.030). At 3 years, the PFS rate was 75% with carfilzomib plus lenalidomide and 65% with lenalidomide alone (hazard ratio 0.64, 95% CI 0.44–0.94; *p*=0.023). At 4 years, the risk of progression or death was significantly reduced in participants given KRd + ASCT versus KCd + ASCT (HR 0.54, 95% CI 0.38–0.78; *p*=0.0008), but similar in those receiving KRd12 and KCd + ASCT.

CONCLUSION: In people with NDMM, significantly more participants treated with KRd versus KCd as induction therapy had a very good partial response or better.

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SAFETY AND EFFECTIVENESS OF WEEKLY CARFILZOMIB, LENALIDOMIDE, DEXAMETHASONE, AND DARATUMUMAB COMBINATION THERAPY FOR PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA:

THE MANHATTAN NONRANDOMIZED CLINICAL TRIAL

JAMA Oncology, 2021 June; 7(6):862–8

AUTHORS: Landgren O, Hultcrantz M, Diamond B, et al.
CENTRE FOR CORRESPONDENCE: Myeloma Program, Sylvester Comprehensive Cancer Center, University of Miami, Miami, Florida, USA

BACKGROUND & AIM: The addition of daratumumab, a monoclonal antibody targeted against CD38, to the established combination of bortezomib, lenalidomide and dexamethasone was recently shown to be safe and to improve outcomes in people with newly diagnosed multiple myeloma (NDMM) who had received high-dose melphalan and autologous stem-cell transplantation. The aim of this study was to assess the clinical activity and safety of adding daratumumab to carfilzomib, lenalidomide and dexamethasone in people with NDMM, in the absence of high-dose melphalan treatment and autologous stem-cell transplantation.

STUDY DESIGN: Non-randomized pilot study.

ENDPOINTS: Primary: minimal residual disease (MRD) negativity rate (with success set at a rate of ≥60%). Secondary endpoints included safety, clinical response rate, and progression-free and overall survival.

METHOD: Adults with NDMM received eight 28-day cycles of carfilzomib (20/56 mg/m^2 on days 1, 8 and 15), lenalidomide (25 mg on days 1–21), dexamethasone (40 mg weekly for cycles 1–4 and then 20 mg) and daratumumab (16 mg/kg on days 1, 8, 15 and 22 for cycles 1 and 2; days 1 and 15 for cycles 3–6; and day 1 for cycles 7 and 8). Following the eight cycles, participants received standard-of-care therapy.

RESULTS: A total of 41 evaluable individuals were enrolled, of whom 20 (49%) had high-risk multiple myeloma at baseline. At a median follow-up of 20.3 months from the start of treatment, 29 participants (71%) were MRD negative and this pilot study was therefore considered successful. The median time to MRD negativity was six cycles (range one to eight cycles). There was no significant difference in the rate of MRD negativity between participants with high- versus standard-risk disease or between older or younger participants (<60 or ≥60 years). The overall response rate was 100%, with 95% of participants having a very good partial response or complete response. At 11 months of the median follow-up, the 1-year progression-free and overall survival rates were 98% and 100%, respectively. The most common grade 3/4 adverse events were neutropenia (27%), rash (9%), lung infection (7%) and increased alanine aminotransferase (4%).

CONCLUSION: The addition of daratumumab to carfilzomib, lenalidomide and dexamethasone was well tolerated and associated with high rates of MRD negativity and progression-free survival in people with NDMM.

https://doi.org/10.1001/jamaoncol.2021.0611

CONSOLIDATION AND MAINTENANCE IN NEWLY DIAGNOSED MULTIPLE MYELOMA

Journal of Clinical Oncology, 2021 November 10; 39(32):3613–22

AUTHORS: Sonneveld P, Dimopoulos MA, Beksac M, et al.
CENTRE FOR CORRESPONDENCE: Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands

BACKGROUND & AIM: The role of consolidation treatment has not been conclusively determined in transplant-eligible individuals with newly diagnosed multiple myeloma (NDMM). The aim of this study was to evaluate consolidation therapy with bortezomib, lenalidomide and dexamethasone (VRD) in this population.

STUDY DESIGN: Randomized, open-label, phase 3 clinical study.

ENDPOINTS: Primary: progression-free survival (PFS). Secondary endpoints included responses and safety.

METHOD: Individuals aged 18–65 years with symptomatic NDMM underwent induction and randomization to an intensification treatment (four cycles of bortezomib, melphalan and prednisone or high-dose melphalan plus autologous stem-cell transplantation), followed by re-randomization to two cycles of consolidation with VRD (n=451) or no consolidation (n=427). All participants received continuous lenalidomide maintenance therapy.

RESULTS: Participants were followed for 74.8 months (interquartile range 64.4–82.3 months) from the second randomization. The median duration of maintenance therapy was similar in the consolidation and no-consolidation arms (35.7 and 31.8 months, respectively; p=0.24). After adjusting for pretreatment, median PFS was significantly longer in participants who received VRD versus no consolidation, at 59.3 versus 42.9 months (hazard ratio 0.81, 95% confidence interval 0.68–0.96; p=0.016). Multivariate regression analysis found that VRD consolidation, response at the time of randomization to consolidation therapy, Revised International Staging Score and platelet count at trial entry were associated with improved PFS (table). The rate of participants with a complete response or better was 34% in the consolidation arm and 18% in the no-consolidation arm (p<0.001). Among 226 participants with a complete response, stringent complete response or very good partial response at the start of maintenance treatment, 74% of VRD-treated participants and 70% of those without consolidation were minimal residual disease-negative. Consolidation with VRD had manageable toxicity.

CONCLUSION: In transplant-eligible individuals with NDMM, VRD consolidation followed by lenalidomide maintenance improved PFS and increased the depth of response compared with lenalidomide maintenance only.

Variables associated with improved PFS on multivariate analysis

Variable	HR (95% CI)	p-value
VRD consolidation versus no consolidation	0.81 (0.68–0.96)	0.015
Very good partial response or better at the time of second randomization	0.70 (0.59–0.84)	<0.001
Revised International Staging Score		
I versus IIa	0.77 (0.63–0.95)	0.015
I versus IIIa	0.52 (0.37–0.73)	<0.001
Platelet count ≥150×10^9/L	0.60 (0.47–0.77)	<0.0001

https://doi.org/10.1200/JCO.21.01045

MAINTENANCE WITH DARATUMUMAB OR OBSERVATION FOLLOWING TREATMENT WITH BORTEZOMIB, THALIDOMIDE, AND DEXAMETHASONE WITH OR WITHOUT DARATUMUMAB AND AUTOLOGOUS STEM-CELL TRANSPLANT IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (CASSIOPEIA):

AN OPEN-LABEL, RANDOMISED, PHASE 3 TRIAL

The Lancet Oncology, 2021 October; 22(10):1378–90

AUTHORS: Moreau P, Hulin C, Perrot A, et al.
CENTRE FOR CORRESPONDENCE: Hematology Clinic, University Hospital Hôtel-Dieu, Nantes, France

BACKGROUND & AIM: In part 1 of the CASSIOPEIA trial, the combination of daratumumab, bortezomib, thalidomide and dexamethasone significantly improved progression-free survival (PFS) and improved the depth of response compared with bortezomib, thalidomide and dexamethasone when used as induction and consolidation therapy in transplant-eligible participants with newly diagnosed multiple myeloma. The aim of part 2 of CASSIOPEIA, reported here, was to investigate survival with daratumumab maintenance therapy versus observation in these participants.

STUDY DESIGN: Two-part, multicentre, randomized, open-label, phase 3 clinical trial.

ENDPOINTS: Primary: PFS after second randomization. Secondary endpoints included the response rate, overall survival and safety.

METHOD: Participants aged 18–65 years who had a partial response or better in part 1 of CASSIOPEIA were randomized to receive either daratumumab (16 mg/kg intravenous every 8 weeks – a reduced dosing frequency compared with standard long-term daratumumab therapy; *n*=442) or observation only (*n*=444) for up to 2 years. Randomization was stratified by the induction treatment and depth of response in part 1 of the study.

RESULTS: At a median follow-up of 35.4 months (interquartile range 30.2–39.9 months) from the second randomization, median PFS was not reached with daratumumab and 46.7 months with observation (hazard ratio 0.53, 95% confidence interval 0.42–0.68; $p<0.0001$). A preplanned analysis using a Cox regression model showed a significant interaction between maintenance and induction and consolidation therapy for PFS ($p<0.0001$). The overall response rate was similar in both groups, at 99.5% with daratumumab and 99.3% with observation, but the rate of complete response or better was significantly higher with daratumumab (73% versus 61%; odds ratio 2.17, 95% CI 1.54–3.07; $p<0.0001$). Median overall survival was not reached in either group. The most common grade 3/4 adverse events reported with daratumumab and observation were lymphopenia (4% and 2%, respectively), hypertension (3% and 2%) and neutropenia (2% and 2%). Serious adverse events occurred in 23% of participants treated with daratumumab and 19% of those undergoing observation. Two treatment-related adverse events in the daratumumab group (septic shock and natural killer-cell lymphoblastic lymphoma) and none in the observation group led to death.

CONCLUSION: In people with newly diagnosed multiple myeloma, daratumumab maintenance therapy every 8 weeks for 2 years was well tolerated and significantly improved the risk of disease progression or death compared with observation alone.

https://doi.org/10.1016/S1470-2045(21)00428-9

POMALIDOMIDE, BORTEZOMIB, AND DEXAMETHASONE AT FIRST RELAPSE IN LENALIDOMIDE-PRETREATED MYELOMA:

A SUBANALYSIS OF OPTIMISMM BY CLINICAL CHARACTERISTICS

European Journal of Haematology, 2022 January; 108(1):73–83

AUTHORS: Richardson PG, Schjesvold F, Weisel K, et al.
CENTRE FOR CORRESPONDENCE: Department of Medical Oncology, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

BACKGROUND & AIM: In the phase 3 OPTIMISMM study, the combination of pomalidomide, bortezomib and dexamethasone (PVd) significantly improved progression-free survival (PFS) versus bortezomib and dexamethasone (Vd) alone in lenalidomide-pretreated participants with relapsed or refractory multiple myeloma. The aim of this post-hoc analysis of OPTIMISMM data was to look at the efficacy and safety of PVd versus Vd by age, renal function and high-risk cytogenetics.

STUDY DESIGN: Post-hoc analysis of a multicentre, randomized, open-label, phase 3 study.

ENDPOINTS: Primary: PFS. Secondary endpoints included the overall response rate and safety.

METHOD: OPTIMISMM randomized adults with lenalidomide- or bortezomib-refractory multiple myeloma to receive PVd (pomalidomide 4 mg/day on days 1–14; bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11 of cycles 1–8 and days 1 and 8 of cycle 9 onwards; and dexamethasone 10 or 20 mg on the days of and after bortezomib administration) or Vd alone. This subgroup analysis looked at data from participants with relapsed disease after one prior line of lenalidomide therapy (n=226) by the subgroups of age ≤65 years (n=100) or >65 years (n=126); creatinine clearance at baseline <60 mL/min (n=63) or ≥60 mL/min (n=163); and high-risk cytogenetic abnormalities (n=32).

RESULTS: Median PFS was significantly longer with PVd versus Vd in participants aged ≤65 years (22.0 versus 13.1 months; hazard ratio 0.49, 95% confidence interval 0.26–0.93; p=0.0258) and >65 years (17.6 versus 9.9 months; HR 0.57, 95% CI 0.34–0.97; p=0.0369) and in those without renal impairment at baseline (22.0 versus 13.1 months; HR 0.45, 95% CI 0.27–0.76; p=0.0020). Median PFS was non-significantly longer with PVd versus Vd in participants with renal impairment (15.1 versus 9.5 months; HR 0.67, 95% CI 0.34–1.34; p=0.2530) and with high-risk cytogenetics at baseline (14.7 versus 9.9 months; HR 0.39, 95% CI 0.13–1.17; p=0.0802). The overall response rate was significantly higher with PVd versus Vd in all participant subgroups (p<0.05). In all subgroups and treatment arms, neutropenia and thrombocytopenia were the most common grade 3/4 haematological treatment-emergent adverse events.

CONCLUSION: PVd showed benefits in lenalidomide-pretreated people at first multiple myeloma relapse regardless of clinically relevant prognostic factors.

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SCREENING, PATIENT IDENTIFICATION, EVALUATION, AND TREATMENT IN PATIENTS WITH GAUCHER DISEASE:

RESULTS FROM A DELPHI CONSENSUS

Molecular Genetics and Metabolism, 2022 February; 135(2):154–62

AUTHORS: Kishnani PS, Al-Hertani W, Balwani M, Göker-Alpan Ö, Lau HA, Wasserstein M, Weinreb NJ, Grabowski G

CENTRE FOR CORRESPONDENCE: Duke University Medical Center, Department of Molecular Genetics and Microbiology, Durham, North Carolina, USA

BACKGROUND & AIM: Gaucher disease is a lysosomal storage disorder caused by mutations in *GBA1* and characterized by a range of signs and symptoms. In the long term, people with this condition are at increased risk of developing B-cell neoplasia, multiple myeloma and monoclonal gammopathy of undetermined significance. The most recent guidelines for Gaucher disease were published in 2013, and subsequent advances in screening, phenotype characterization and treatment have been incorporated using Delphi approaches. The current article reports the results of a Delphi consensus exercise to address newborn screening, diagnostic evaluation and treatment in people with Gaucher disease.

ARTICLE TYPE: Clinical guidelines.

FINDINGS: A list of 138 statements was prepared from a literature review and sent to an independent panel of 16 individuals with expertise in Gaucher disease. Panel members scored each statement on a 5-point Likert scale, and two rounds of review and a final check produced a final set of 65 statements achieving consensus, on each of which all panel members agreed or strongly agreed.

Newborn screening is supported because earlier onset and progression of Gaucher disease are associated with more severe disease and an increased morbidity risk, and a diagnosis is often delayed following the first appearance of clinical and laboratory signs. Some individuals will not need immediate treatment but should be followed up annually. A definitive diagnosis requires genetic testing of the whole *GBA1* sequence to confirm an initial lysosomal glucocerebrosidase evaluation, and laboratory testing is recommended for anyone with signs such as unexplained splenomegaly, anaemia or thrombocytopenia, as well as those with Ashkenazi Jewish genetic ancestry. The recommended assessments for an individual with Gaucher disease include quantitative volumetric imaging of the liver and spleen, and assessments of bone mineral density and skeletal abnormalities, with additional testing for those with suspected neuronopathic disease.

People with Gaucher disease should be managed by a multidisciplinary team. Several organ-specific treatment goals were supported by the panel, as well as goals relating to quality of life. There are currently no biomarkers to predict when to start treatment, but enzyme replacement therapy may prevent the development of irreversible pathology in children with progressing or significant signs of Gaucher disease.

CONCLUSIONS: Guidance is presented on newborn screening, patient assessment, treatment goals, and the use of current treatments and adjunctive interventions in Gaucher disease.

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CARFILZOMIB, LENALIDOMIDE, AND DEXAMETHASONE FOLLOWED BY LENALIDOMIDE MAINTENANCE FOR PREVENTION OF SYMPTOMATIC MULTIPLE MYELOMA IN PATIENTS WITH HIGH-RISK SMOLDERING MYELOMA:

A PHASE 2 NONRANDOMIZED CONTROLLED TRIAL

JAMA Oncology, 2021 November 1; 7(11):1678–85

AUTHORS: Kazandjian D, Hill E, Dew A, et al.
CENTRE FOR CORRESPONDENCE: Multiple Myeloma Program, Sylvester Comprehensive Cancer Center, University of Miami, Miami, Florida, USA

BACKGROUND & AIM: In people with smouldering myeloma who are at high risk of developing multiple myeloma, treatment with lenalidomide has been shown to decrease the risk of progression versus observation alone. The aim of this study was to investigate whether a novel triplet regimen of carfilzomib, lenalidomide and dexamethasone (KRd), followed by lenalidomide maintenance, could increase the rate of minimal residual disease (MRD) negativity and decrease disease progression in people with early high-risk smouldering myeloma.

STUDY DESIGN: Single-arm, single-centre, non-randomized, controlled, phase 2 trial.

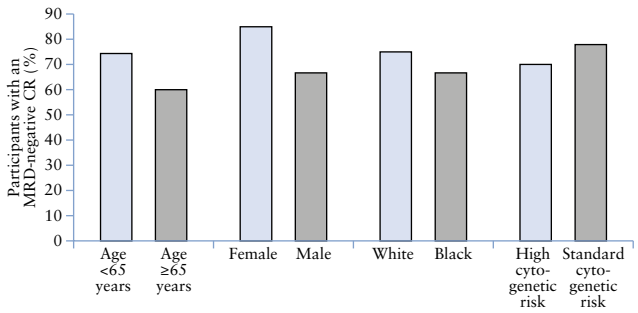
ENDPOINTS: Primary: MRD-negative complete response (CR) rate. Secondary: duration of MRD-negative CR; progression to multiple myeloma; safety.

METHOD: Individuals with high-risk smouldering myeloma (n=54) received eight 28-day cycles of carfilzomib (20 mg/m^2 for the first two doses, then 36 mg/m^2 on days 1, 2, 8, 9, 15 and 16), dexamethasone (20 mg twice weekly for cycles 1–4; 10 mg twice weekly for cycles 5–8) and lenalidomide (25 mg on days 1–21), followed by twenty-four 28-day cycles of maintenance lenalidomide (10 mg on days 1–21).

RESULTS: At the time of data cut-off, the median potential follow-up time was 31.9 months (range 6.7–102.9 months). The MRD-negative CR rate was 70.4%, and the median sustained duration of MRD-negative CR was 5.5 years. High MRD-negative CR rates (≥60%) were seen irrespective of age, sex, race/ethnicity, cytogenetic risk or the presence of high-risk cytogenetics (figure). Only two participants developed multiple myeloma (osteolytic lesions while off-treatment in both). The 5- and 8-year probabilities of being free from progression to multiple myeloma were both 91.2%, and there were no deaths. A total of 21 participants (38.9%) experienced grade 3 non-haematological adverse events, which included thromboembolism (n=2, 3.7%), rash (n=4, 7.4%), hyperglycaemia (n=3, 5.6%) and lung infection (n=3, 5.6%). There were no grade 4 events and no participants died.

CONCLUSION: In participants with high-risk smouldering myeloma, treatment with KRd followed by lenalidomide maintenance resulted in a high rate of MRD-negative CRs and delayed progression to multiple myeloma.

MRD-negative CRs in participant subgroups



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MCT1 IS A PREDICTIVE MARKER FOR LENALIDOMIDE MAINTENANCE THERAPY IN MULTIPLE MYELOMA

Blood Advances, 2022 January 25; 6(2):515–20

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BACKGROUND & AIM: Lenalidomide maintenance therapy has been shown to improve the outcomes of people with multiple myeloma (MM). However, the benefits of treatment vary among studies, and predictive markers of response have not yet been identified. The antimyeloma effects of immunomodulatory drugs such as lenalidomide, thalidomide and bortezomib occur by destabilizing MCT1 and CD147, which are upregulated in MM. The aim of the current study was to investigate whether gene-expression levels of *MCT1* and *CD147* are associated with response to immunomodulatory maintenance therapy in people with MM.

STUDY DESIGN: Cohort study.

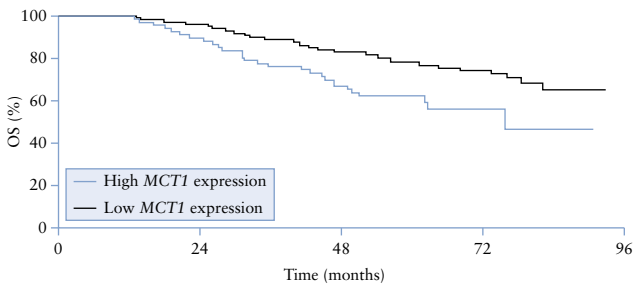
ENDPOINTS: Progression-free survival (PFS); overall survival (OS).

METHOD: The study included 654 participants with MM who underwent high-dose melphalan treatment and autologous stem-cell transplantation, following which they received maintenance therapy with lenalidomide (*n*=455), thalidomide (*n*=98) or bortezomib (*n*=101) as part of a phase 3 clinical trial. CD138-purified myeloma cell samples from these individuals were assessed using gene-expression profiling to determine the expression of *MCT1* and *CD147*, and the results were validated using RNA sequencing. *MCT1* and *CD147* expression were then correlated with PFS and OS data.

RESULTS: Among participants who received lenalidomide maintenance therapy, those with high *MCT1* gene-expression levels had significantly shorter median PFS than participants with low *MCT1* expression (31.9 versus 48.2 months, *p*=0.03). High *MCT1* expression in this group was also associated with shorter median OS (75.9 months versus not reached, *p*=0.001; figure). Similarly, among participants who received thalidomide, those with high *MCT1* expression had significantly shorter OS (83.6 months versus not reached, *p*=0.03), although the difference in PFS did not reach significance (34.8 versus 43.7 months, *p*=0.23). In contrast, high *MCT1* expression was not predictive among participants receiving bortezomib maintenance therapy. In human MM cell lines, *in vitro* and in a xenograft model, *MCT1* overexpression significantly reduced the efficacy of lenalidomide.

CONCLUSION: *MCT1* expression was found to predict the response to lenalidomide maintenance therapy in people with MM.

OS with lenalidomide maintenance therapy by *MCT1* expression



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IDENTIFICATION OF PATIENTS AT HIGH RISK OF SECONDARY EXTRAMEDULLARY MULTIPLE MYELOMA DEVELOPMENT

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BACKGROUND & AIM: Some individuals with multiple myeloma (MM) develop extramedullary disease (EMD), in which malignant cells migrate beyond the bone marrow to infiltrate the soft tissues. EMD can be present at the time of MM diagnosis (primary EMD) or at the time of relapse (secondary EMD). Secondary EMD in particular is associated with a poor prognosis, and it is therefore important to identify people at high risk of this condition as early as possible. The aim of this study was to identify risk factors for developing secondary EMD in people with MM.

STUDY DESIGN: Real-life retrospective study.

ENDPOINTS: Risk factors for the development of EMD; effect of EMD on progression-free survival (PFS) and overall survival (OS).

METHOD: Data from 4985 people diagnosed with MM were examined, and individuals who developed secondary EMD (n=234) were compared with those with no EMD (n=2092). Logistic regression analysis was used to identify associations of baseline characteristics at MM diagnosis with EMD occurrence at MM relapse. Differences in PFS and OS in participants with future EMD and those who did not develop EMD were analysed using Kaplan–Meier methodology. The prognostic significance of secondary EMD was investigated using a multivariable Cox proportional hazards model.

RESULTS: In people with newly diagnosed MM, those aged 65 years or younger (odds ratio 4.38, 95% confidence interval 2.46–7.80; p<0.0001) or with lactate dehydrogenase levels of more than 5 µkat/l (OR 2.07, 95% CI 1.51–2.84; p<0.0001), extensive osteolytic activity (OR 2.21, 1.54–3.15, p<0.001), immunoglobulin A M-protein type MM (OR 1.53, 95% CI 1.11–2.11; p=0.009) or non-secretory MM (OR 2.83, 95% CI 1.32–6.04; p=0.007) were significantly more likely to develop EMD. Median PFS and OS were significantly shorter in people with newly diagnosed MM who subsequently developed EMD than in those who did not (median PFS 13.8 versus 18.8 months, p=0.006; median OS 26.7 versus 58.7 months, p<0.001). On multivariate analysis, secondary EMD was an independent risk factor for both PFS (hazard ratio 1.39, 95% CI 1.06–1.81, p=0.016) and OS (HR 1.61, 95% CI 1.20–2.15, p=0.001) in people with relapsed/refractory MM.

CONCLUSION: Specific patient- and disease-related factors were identified that were associated with the development of EMD in people with MM.

https://doi.org/10.1111/bjh.17925

PROGNOSTIC SIGNIFICANCE OF ACQUIRED 1Q22 GAIN IN MULTIPLE MYELOMA

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BACKGROUND & AIMS: People whose multiple myeloma has 1q22 gain at diagnosis often present with more aggressive clinical features and disease, and experience shorter survival, than those whose disease does not have this abnormality. However, the prognostic significance of acquired 1q22 gain is unclear. The aims of this study were to examine the clinical characteristics and outcomes of people acquiring 1q22 gain over time, and to identify risk factors for acquiring 1q22 gain.

STUDY DESIGN: Retrospective database study.

ENDPOINTS: Incidence of acquired 1q22 gain; risk factors for 1q22 gain acquisition; progression-free survival (PFS) and overall survival (OS), and associated factors.

METHOD: Data were examined from 1041 people with multiple myeloma, and those without 1q22 gain at diagnosis but who acquired it during follow-up were identified (n=63). Each of these individuals was matched with a control participant without 1q22 gain at any timepoint (n=63). A further cohort of individuals with 1q22 gain at multiple myeloma diagnosis was also identified (n=126), and survival outcomes were compared among the cohorts. Factors at 1q22 acquisition associated with PFS and OS were identified using a Cox proportional hazards model.

RESULTS: The incidence of acquired 1q22 gain was 6.1%, and the median time to detection was 5.0 years (range 0.7–11.7 years). In people who acquired 1q22 gain, the most common FISH abnormalities at diagnosis were trisomies (52.4%), monosomy 13 (38.1%) and t(11;14) (22.2%); 12.7% had high-risk aberrations and 11.1% had del(17p). Median PFS following first-line therapy was similar in people with and without acquired 1q22 gain (29.5 versus 31.4 months, respectively; p=0.34), but significantly shorter in those with acquired 1q22 gain versus 1q22 gain at diagnosis (29.5 versus 31.2 months, p=0.04). Median OS was 10.9 years in the acquired 1q22 gain group, versus 13.0 years in the control group (p=0.02) and 6.3 years in those with 1q22 gain at diagnosis (p=0.01). The only predictor of acquiring 1q22 gain was the presence of high-risk FISH abnormalities at baseline (odds ratio 5.40, 95% confidence interval 1.68–17.29).

CONCLUSION: In people with multiple myeloma, acquiring 1q22 gain over time was associated with shorter OS compared with those who did not acquire 1q22 gain.

https://doi.org/10.1002/ajh.26391

PRIMARY PLASMA CELL LEUKEMIA:
CONSENSUS DEFINITION BY THE INTERNATIONAL MYELOMA WORKING GROUP ACCORDING TO PERIPHERAL BLOOD PLASMA CELL PERCENTAGE

Blood Cancer Journal, 2021 December 2; 11(12):192

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BACKGROUND & AIM: Primary plasma cell leukaemia (PCL) is considered an ultra–high-risk disease and early diagnosis is essential. The diagnostic criteria for PCL require an absolute plasma cell count of more than 2×10^9/L as well as more than 20% circulating plasma cells. However, there are concerns that these criteria are too restrictive. The aim of this article was to reconsider the diagnostic criteria for primary PCL in people otherwise meeting the diagnostic criteria for multiple myeloma.

STUDY DESIGN: Consensus recommendation.

FINDINGS: A review of the literature identified two retrospective studies assessing the number of circulating plasma cells in peripheral blood that should be used to define PCL, both of which investigated whether a lower cut-off (e.g. 5%) has the same prognostic value as the 20% cut-off used historically. One study looked at 100 people with PCL from five university hospitals in Catalonia, Spain (versus 382 control individuals without circulating plasma cells), while the other assessed 176 people with PCL from the US Mayo Clinic (versus 9724 historical control individuals). In both studies, the plasma cell percentage was calculated from morphological evaluation of peripheral-blood smears, and the primary outcome was overall survival (OS).

In the Spanish study, median OS was 47 months in people with 0% circulating plasma cells, 50 months in those with 1–4%, 6 months in those with 5–20% and 14 months in those with more than 20%. People with 5% or more circulating plasma cells had significantly shorter OS than those with fewer than 5% (1.1 versus 4.4 years; relative risk 4, 95% confidence interval 2.1–7.3; $p<0.001$). In multivariate analysis, the presence of 5–20% circulating plasma cells was an independent predictor of shorter OS (RR 4.9, 95% CI 2.6–9.3). In the US study, median OS was 53, 17, 13 and 13 months for people with 0%, 1–4%, 5–19% and 20% or more circulating plasma cells, respectively. Those with more than 5% again had significantly shorter OS (1.17 versus 4.8 years, $p<0.001$).

CONCLUSION: These findings indicate that a diagnosis of PCL in people with symptomatic multiple myeloma should be defined by the presence of 5% or more circulating plasma cells in peripheral blood smears.

https://doi.org/10.1038/s41408-021-00587-0

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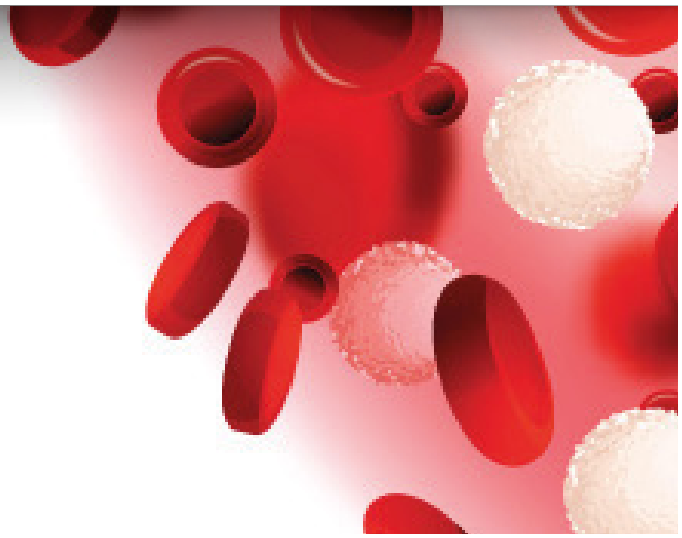

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