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Journal of Clinical Oncology, 2022 September 1; 40(25):2901–12

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Medical Writers (this issue)
Milena Braga-Basaria
Derek Collett
Kathy Croom
David Newton
Sue Peter

Art Design
Jan van Halm

Layout and Printing
Drukmeesters,
Zwijndrecht, the Netherlands

Publishing Director
Evelien Enter

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HOW TO EVALUATE AND TREAT THE SPECTRUM OF TMA SYNDROMES IN PREGNANCY

Hematology: ASH Education Program, 2021 December 10; 2021(1):545–51

AUTHOR: Scully M
CENTRE: Department of Haematology, University College London Hospitals NHS Foundation Trust and Cardiometabolic Programme-NIHR UCLH/UC BRC, London, UK

BACKGROUND & AIM: Thrombotic microangiopathies (TMAs) during pregnancy can have an adverse effect on maternal and fetal outcomes. In particular, thrombotic thrombocytopenic purpura (TTP) and complement-mediated haemolytic-uraemic syndrome (CM-HUS) are acute, life-threatening disorders that can present during pregnancy (as opposed to being specific to pregnancy) and need prompt diagnosis and treatment. The aim of this review was to discuss the diagnosis and management of TMAs during pregnancy.

TYPE OF ARTICLE: Expert review.

FINDINGS: In pregnant women, TTP and CM-HUS can be confused with pregnancy-specific TMAs such as pregnancy-induced hypertension, pre-eclampsia and HELLP (haemolysis, elevated liver enzymes and low platelets). Differentiating these conditions is vital, as TTP and CM-HUS need urgent and specific therapy. Of note, TTP can occur at any stage of pregnancy, but is most common in the third trimester or postpartum; CM-HUS occasionally occurs during the first trimester, but is most often seen postpartum.

The diagnosis of TMA in pregnancy is suggested by a platelet count of less than 100×10^9/L, raised lactate dehydrogenase levels, and blood film findings suggesting anaemia, polychromasia, thrombocytopenia and fragmented red blood cells. Other laboratory analysis can help with the diagnosis. Although thrombocytopenia, high blood pressure and end-organ damage can occur with any TMA, worsening acute kidney injury (even in the absence of thrombocytopenia) suggests CM-HUS, whereas neurological findings and severely reduced ADAMTS-13 levels point to TTP.

Pregnancy-related TMAs generally normalize within 48 hours after delivery. If CM-HUS or TTP is considered a possibility then plasma exchange should be started promptly. Specific therapies include the complement inhibitor eculizumab for CM-HUS, and ADAMTS-13 replacement and immunosuppression for TTP. Control of blood pressure and supportive therapy, such as renal replacement therapy, should be provided as necessary.

CM-HUS and TTP can reoccur in subsequent pregnancies. A multidisciplinary approach to monitoring the mother and baby in later pregnancies is advised, involving obstetricians, fetal medicine units and neonatologists. Regular fetal scans and Doppler uterine artery flow measurements are important. Separate management pathways are provided for immune-mediated and congenital TTP, including guidance on when to start ADAMTS-13 replacement.

CONCLUSIONS: It can be difficult to differentiate CM-HUS and TTP that occur during pregnancy from specific pregnancy-related TMAs. This article provides guidance on diagnosing and treating TMAs during pregnancy, and on managing subsequent pregnancies.

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IN-DEPTH PHENOTYPING FOR CLINICAL STRATIFICATION OF GAUCHER DISEASE

Orphanet Journal of Rare Diseases, 2021 October 14;16(1):431

AUTHORS: D'Amore S, Page K, Donald A, Taiyari K, Tom B, Deegan P, Tan CY, Poole K, Jones SA, Mehta A, Hughes D, Sharma R, Lachmann RH, Chakrapani A, Geberhiwot T, Santra S, Banka S, Cox TM and the MRC GAUCHERITE Consortium
CENTRE FOR CORRESPONDENCE: Department of Medicine, University of Cambridge, Cambridge, UK

BACKGROUND & AIMS: Gaucher disease is an ultra-rare genetic disorder of sphingolipid metabolism that can affect the nervous system, skeletal system, spleen, liver and lungs. Molecular therapies can be effective, particularly if provided early in the disease process. The aims of this study were to characterize the course of Gaucher disease and to explore the effects of medication and other interventions in a national cohort of people with the condition, with a focus on skeletal and neurological manifestations.

STUDY DESIGN: Cohort study.

ENDPOINTS: Clinical characteristics and course of disease; effect of treatment.

METHOD: All individuals with confirmed type 1 (non-neuronopathic) or type 3 (chronic neuronopathic) Gaucher disease in the UK were invited to participate in the Gaucher Investigative Therapy Evaluation (GAUCHERITE) between 2015 and 2017, with a pre-set target of 250 participants (representing around 85% of known UK patients). Retrospective and prospective clinical, laboratory, radiological and molecular information were recorded in the GAUCHERITE database, and biological samples were banked.

RESULTS: Study participants (n=250) were aged 5–87 years, and 223 had type 1 Gaucher disease and 27 had type 3. Participants were followed for a median of 17.3 years. Skeletal manifestations were common, with 131/201 participants reporting bone pain. Among all 250 individuals, symptomatic osteonecrosis occurred in 76 participants and fragility fractures in 37. First fragility fractures occurred earlier in participants with type 3 versus type 1 disease (median age 20 versus 44 years), and women had a greater risk of fracture than men. A quarter of all participants had undergone splenectomy. Splenectomy increased the risk of fragility fractures and symptomatic osteonecrosis three-fold and the risk of orthopaedic surgery two-fold. Within 6 months of study enrolment, 243 participants were receiving Gaucher-specific therapies. Gaucher-specific molecular therapy reduced the risk of symptomatic osteonecrosis (p<0.001), but not the risk of fragility fractures. The most common neurological sign in participants with type 3 disease was horizontal saccadic eye movement defect (27/27 participants). Deep phenotyping of a subgroup of 40 participants with type 1 (non-neuronopathic) disease found that 16 had signs compatible with neuronopathic Gaucher disease and two had Parkinson's disease.

CONCLUSIONS: Gaucher disease was found to cause variable phenotypic manifestations, including systemic, skeletal and neurological signs. Splenectomy increased the risk of osseous complications, while molecular therapy reduced the risk of some osseous complications.

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RISK STRATIFIED MANAGEMENT APPROACHES FOR SMOULDERING MULTIPLE MYELOMA:

CLINICAL RESEARCH BECOMES CLINICAL PRACTICE

The Lancet Haematology, 2022 February; 9(2):e162–5

AUTHORS: Lonial S, Rajkumar SV, Mateos MV
CENTRES: Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, Georgia; Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA; Department of Hematology, and Center for Cancer Research, University Hospital of Salamanca, Salamanca, Spain

BACKGROUND & AIM: Smouldering multiple myeloma (MM) has historically been managed with observation alone because, across all individuals, the risks of treatment outweigh those of disease progression. However, increasing numbers of clinical trials are looking at new treatments for smouldering MM, with the goals of reducing the risk of progression and organ damage, and preventing the need for more intensive treatment. The aim of this article was to discuss risk-stratified management approaches for smouldering MM based on the current evidence.

ARTICLE TYPE: Review.

FINDINGS: Two phase 3 trials have demonstrated the benefits of early intervention in people with smouldering MM who are in the highest risk group. In the PETHEMA trial, participants with high-risk disease who received early treatment with lenalidomide plus dexamethasone for 2 years had a significantly longer time to development of MM than those managed with observation only, and significantly longer overall survival. In the ECOG E3A06 trial, the 3-year progression-free survival rate was 91% in high- or intermediate-risk individuals treated with lenalidomide alone, compared with 66% in those managed with observation (p=0.002). The use of a more robust method of risk stratification (incorporating the serum free light-chain ratio, serum M-protein concentration and bone marrow plasma cell involvement) led to a greater than 90% reduction in end-organ damage with early therapy. Other trials are currently investigating whether early therapy can cure some people with smouldering MM.

The authors recommend using the Mayo 2018 criteria to stratify people with smouldering MM according to risk. These criteria define individuals as being high risk (with a median time to progression of 2 years) if they have more than 20% bone marrow plasma cells, more than 2 g/dL M-protein or a serum free light-chain ratio of more than 20. The clinical trial evidence suggests that individuals fulfilling these criteria could benefit from preventative therapy with lenalidomide with or without dexamethasone. In addition, people with an evolving pattern of disease may experience greater benefit from MM therapies than from a preventative approach, while those who have been stable for more than 3 years without therapy and with no progression have indolent disease and do not require preventative treatment.

CONCLUSION: Modern risk assessment and new treatments allow the optimization of early therapy for people with smouldering MM.

https://doi.org/10.1016/S2352-3026(21)00335-5

CONSENSUS GUIDELINES AND RECOMMENDATIONS FOR INFECTION PREVENTION IN MULTIPLE MYELOMA:

A REPORT FROM THE INTERNATIONAL MYELOMA WORKING GROUP

The Lancet Haematology, 2022 February; 9(2):e143–61

AUTHORS: Raje NS, Anaissie E, Kumar SK, et al.
CENTRE FOR CORRESPONDENCE: Center for Multiple Myeloma, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts, USA

BACKGROUND & AIM: Infection is the leading cause of death among people with multiple myeloma (MM). People with MM have an increased risk of infection for several reasons, including immunosuppression resulting from both the disease itself and its treatment. The aim of this article was to review and provide consensus recommendations (developed by a panel of 36 experts) on the risk of infection and preventing infectious complications in people with MM.

ARTICLE TYPE: Consensus guidelines and recommendations.

FINDINGS: People with MM are at the highest risk of infection in the 3 months following diagnosis and when undergoing treatment for relapsed or refractory disease; in particular, those with newly diagnosed disease have high rates of potentially preventable infections, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. The increased risk in those with newly diagnosed MM is due to global immunoparesis (including B-cell dysfunction, hypogammaglobulinaemia, disrupted T-cell diversity, and alterations to dendritic and natural killer cell activity). A wide range of treatments are available for MM, and many of these cause immunosuppression and are associated with an increased risk of infection. Most infections in MM are caused by viruses (which typically present as influenza and herpes zoster) and bacteria (which most commonly present as pneumonia and bacteraemia).

The panel recommends considering antibacterial prophylaxis with levofloxacin during periods of increased infectious risk, as well as specific prophylactic treatments depending on the MM therapy being received. Annual immunization with inactivated influenza vaccine is also recommended (activated vaccines are not recommended for this population). The response to vaccination may be influenced by the person's state of immunosuppression or the use of chemotherapy, and the best protection is achieved when vaccines are given at an early stage of disease. The response may be improved by single-agent lenalidomide. Revaccination is recommended 6–12 months after autologous haematopoietic stem-cell transplantation, as well as vaccination with the recombinant zoster vaccine. The panel also suggests that the recombinant zoster vaccine should be extended to all people with MM. Recommendations are made for the close contacts of people with MM as well as healthcare providers, and in regard to travelling to endemic areas of infection.

CONCLUSIONS: Infections are an important cause of morbidity and mortality in people with MM. These recommendations can help in developing an individual-specific plan for their prevention.

https://doi.org/10.1016/S2352-3026(21)00283-0

MELFLUFEN OR POMALIDOMIDE PLUS DEXAMETHASONE FOR PATIENTS WITH MULTIPLE MYELOMA REFRACTORY TO LENALIDOMIDE (OCEAN):

A RANDOMISED, HEAD-TO-HEAD, OPEN-LABEL, PHASE 3 STUDY

The Lancet Haematology, 2022 February; 9(2):e98–110

AUTHORS: Schjesvold FH, Dimopoulos MA, Delimpasi S, et al.; on behalf of the OCEAN (OP-103) Investigators
CENTRE FOR CORRESPONDENCE: University of Oslo; Oslo Myeloma Center, Oslo University Hospital, Oslo, Norway

BACKGROUND & AIM: The alkylating peptide–drug conjugate melphalan flufenamide (melflufen) has shown clinical activity and manageable safety when given with dexamethasone to participants with relapsed/refractory multiple myeloma (RRMM) in a phase 2 trial. The aim of this study was to directly compare melflufen plus dexamethasone with pomalidomide plus dexamethasone in people with previously treated multiple myeloma.

STUDY DESIGN: International, randomized, open-label, phase 3 study.

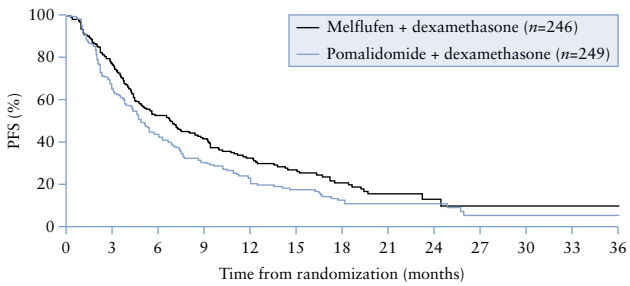
ENDPOINTS: Primary: progression-free survival (PFS). Key secondary endpoints included overall survival and safety.

METHOD: Adults with RRMM who had received two to four previous lines of therapy (including lenalidomide and a proteasome inhibitor) were given dexamethasone (40 mg orally on days 1, 8, 15 and 22 of each cycle) plus 28-day cycles of either melflufen (40 mg intravenously over 30 min, day 1 of each cycle; *n*=246) or pomalidomide (4 mg orally daily, days 1–21 of each cycle; *n*=249) until disease progression, unacceptable toxicity or study withdrawal.

RESULTS: At a median follow-up of 15.5 months (interquartile range 9.4–22.8 months) in the melflufen group and 16.3 months (IQR 10.1–23.2 months) in the pomalidomide group, median PFS was significantly longer in the melflufen arm, at 6.8 versus 4.9 months (hazard ratio 0.79, 95% confidence interval 0.64–0.98; *p*=0.032; figure). There was no difference in overall survival between the two groups. The most common grade 3/4 treatment-emergent adverse events (TEAEs) were thrombocytopenia (melflufen 63% versus pomalidomide 11%), neutropenia (54% versus 41%) and anaemia (43% versus 18%). There were similar numbers of serious TEAEs in the two treatment groups (42% in the melflufen group versus 46% in the pomalidomide group). Two fatal TEAEs were considered possibly treatment related in the melflufen group (one acute myeloid leukaemia, one pancytopenia and acute cardiac failure) and four in the pomalidomide group (two pneumonia, one myelodysplastic syndromes, one COVID-19 pneumonia).

CONCLUSION: Melflufen plus dexamethasone showed superior PFS to pomalidomide plus dexamethasone in people with RRMM, with acceptable toxicity.

PFS in people with RRMM treated with dexamethasone plus melflufen or pomalidomide



https://doi.org/10.1016/S2352-3026(21)00381-1

ISATUXIMAB PLUS POMALIDOMIDE AND LOW-DOSE DEXAMETHASONE VERSUS POMALIDOMIDE AND LOW-DOSE DEXAMETHASONE IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (ICARIA-MM):

FOLLOW-UP ANALYSIS OF A RANDOMISED, PHASE 3 STUDY

The Lancet Oncology, 2022 March; 23(3):416–27

AUTHORS: Richardson PG, Perrot A, San-Miguel J, Beksac M, Spicka I, Leleu X, Schjesvold F, Moreau P, Dimopoulos MA, Huang JS, Minarik J, Cavo M, Prince HM, Malinge L, Dubin F, van de Velde H, Anderson KC

CENTRE FOR CORRESPONDENCE: Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

BACKGROUND & AIM: Isatuximab is an IgG1 monoclonal antibody that targets a specific epitope of CD38 and induces direct apoptosis and activation of natural killer cells, as well as dose-dependent inhibition of CD38 ectoenzyme activity. The ICARIA-MM study is evaluating the effect of adding isatuximab to pomalidomide–dexamethasone in people with relapsed/refractory multiple myeloma (RRMM). The primary analysis of ICARIA-MM showed significantly improved progression-free survival with the addition of isatuximab. The aim of this paper was to report survival results after an additional 24 months of follow-up.

STUDY DESIGN: Prespecified interim analysis of a prospective, randomized, multicentre, open-label, phase 3 study.

ENDPOINTS: Overall survival at 24 months (a key secondary endpoint of ICARIA-MM); progression-free survival per investigator assessment; safety.

METHOD: In ICARIA-MM, adults with RRMM who had received at least two previous lines of therapy and who had not responded to lenalidomide plus a proteasome inhibitor were given pomalidomide plus dexamethasone either alone (control group; *n*=153) or with the addition of isatuximab (*n*=154). Isatuximab (10 mg/kg) was administered intravenously on days 1, 8, 15 and 22 of the first 4-week cycle and days 1 and 15 of subsequent cycles. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent.

RESULTS: At a median follow-up of 35.3 months (interquartile range 33.5–37.4 months), the median treatment duration was 47.6 weeks (IQR 19.1–94.6 weeks) in the isatuximab group and 24.0 weeks (IQR 11.1–53.9 weeks) in the control group. At this point, compared with the control group, participants in the isatuximab group had significantly longer median overall survival (24.6 versus 17.7 months; hazard ratio 0.76, 95% confidence interval 0.57–1.01; p=0.028) and progression-free survival (11.1 versus 5.9 months; HR 0.60, 95% CI 0.46–0.78; p<0.0001). No new safety concerns were identified with isatuximab. The most common grade 3 or worse treatment-emergent adverse events were neutropenia (50% in the isatuximab group and 35% in the control group), pneumonia (23% and 21%) and thrombocytopenia (13% and 12%). Serious adverse events were seen in 73% of participants in the isatuximab group and 60% in the control group.

CONCLUSION: In people with RRMM, adding isatuximab to pomalidomide plus dexamethasone therapy was associated with significantly longer overall survival.

https://doi.org/10.1016/S1470-2045(22)00019-5

MASS SPECTROMETRY VS IMMUNOFIXATION FOR TREATMENT MONITORING IN MULTIPLE MYELOMA

Blood Advances, 2022 June 14; 6(11):3234–39

AUTHORS: Puig N, Sanfeliciano TC, Agullo Roca C, et al.
CENTRE FOR CORRESPONDENCE: Hospital Universitario de Salamanca, Salamanca, Spain

BACKGROUND & AIM: M-protein is commonly used as a biomarker to assess response to treatment in people with multiple myeloma (MM). It is evaluated in serum and urine samples using electrophoresis or immunofixation (IFE), but the introduction of highly active therapies means that M-protein is now frequently undetectable during and after treatment, and more sensitive techniques are therefore needed for treatment monitoring. The aim of this study was to compare mass spectrometry (MS) with IFE for detecting M-protein in the serum of people with MM.

STUDY DESIGN: Cohort study.

ENDPOINT: M-protein detection.

METHOD: The study included 223 individuals with newly diagnosed, transplant-eligible MM who were undergoing induction therapy, autologous stem-cell transplantation (ASCT) and consolidation therapy as part of a phase 3, open-label trial. Serum samples were collected at baseline and after induction (*n*=183), ASCT (*n*=173) and consolidation (*n*=173), and the presence of M-protein was assessed using both MS (EXENT system plus measurement of free light chains) and IFE, with pooled normal serum as a negative control. The results were compared between the two techniques, and their ability to predict progression-free survival was assessed using the Kaplan–Meier method and log-rank test.

RESULTS: MS and IFE produced fully matched M-protein results in 183 out of 223 samples (82.1%); in most of the remaining 40 samples, MS provided additional information that was not detected by IFE. There was also good concordance between the two techniques during treatment monitoring, with matching results in 82% of samples post-induction, 86% post-ASCT and 84% post-consolidation. Where there was discordance, this was usually due to a positive MS but negative IFE result. Both techniques were able to discriminate between two subgroups of participants with significantly different progression-free survival post-induction and post-ASCT, but only MS could discriminate these subgroups post-consolidation.

CONCLUSION: MS was found to be more sensitive than IFE in detecting M-protein in people with MM at baseline and during treatment, and could more accurately predict progression-free survival.

https://doi.org/10.1182/bloodadvances.2021006762

INCIDENCE AND MANAGEMENT OF CAR-T NEUROTOXICITY IN PATIENTS WITH MULTIPLE MYELOMA TREATED WITH CILTACABTAGENE AUTOLEUCEL IN CARTITUDE STUDIES

Blood Cancer Journal, 2022 February 24; 12(2):32

AUTHORS: Cohen AD, Parekh S, Santomasso BD, Gállego Pérez-Larraya J, van de Donk NW, Arnulf B, Mateos MV, Lendvai N, Jackson CC, De Braganca KC, Schecter JM, Marquez L, Lee E, Cornax I, Zudaire E, Li C, Olyslager Y, Madduri D, Varsos H, Pacaud L, Akram M, Geng D, Jakubowiak A, Einsele H, Jagannath S
CENTRE FOR CORRESPONDENCE: Mount Sinai Medical Center, New York, New York, USA

BACKGROUND & AIMS: Ciltacabtagene autoleucel (cilta-cel) is a chimeric antigen receptor (CAR) T-cell therapy that showed good efficacy in the phase 1b/2 CARTITUDE-1 trial in participants with heavily pretreated relapsed/refractory multiple myeloma. However, movement and neurocognitive treatment-emergent adverse events (MNTs) were seen in 5% of participants. The aims of this study were to assess factors associated with MNTs in CARTITUDE-1, and to evaluate the effectiveness of strategies implemented to reduce their incidence.

STUDY DESIGN: Safety analysis of an open-label, phase 1b/2 study.

ENDPOINTS: Factors associated with MNTs; incidence of MNTs.

METHOD: In CARTITUDE-1, people with relapsed/refractory multiple myeloma received cilta-cel as a single infusion on day 1, and were monitored for safety until 2 years after the last participant was dosed. A safety management team evaluated participants with MNTs to identify and implement changes to ongoing studies within the CARTITUDE programme.

RESULTS: This safety analysis included neurotoxicity data from 97 CARTITUDE-1 participants with a median follow-up of 18 months. CAR T-cell neurotoxicities occurred in 20.6% of participants, including nine grade 3/4 events (9.3%) and one grade 5 event (1.0%). Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 16 individuals (16%), other CAR T-cell neurotoxicities in 12 (12.4%) and both in eight (8.2%). Factors potentially associated with MNTs on logistic regression analysis included high baseline tumour burden (odds ratio 9.1), grade 2 or worse cytokine release syndrome (OR 15.6), ICANS (OR 26.7), high CAR T-cell expansion/persistence (OR 48.6) and a high absolute lymphocyte count at day 28 (OR 3.4). Preventative strategies implemented across the CARTITUDE programme included placing fewer restrictions on the choice of bridging therapy, with the aim of reducing baseline tumour burden. Monitoring strategies included using a novel handwriting tool to detect neurotoxicity symptoms early, and introducing an extended monitoring and reporting time for CAR T-cell neurotoxicities. Management strategies included early and aggressive supportive care for any-grade ICANS, and tocilizumab for any-grade ICANS with concurrent cytokine release syndrome. Among more than 150 individuals who were given cilta-cel in the clinical development programme after these strategies were implemented, only one had developed MNTs as of the data cut-off.

CONCLUSION: In people with multiple myeloma treated with cilta-cel, new preventative, monitoring and management strategies reduced the incidence of MNTs from 5% to less than 1%.

https://doi.org/10.1038/s41408-022-00629-1

DARATUMUMAB PLUS LENALIDOMIDE AND DEXAMETHASONE IN TRANSPLANT-INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA:

FRAILTY SUBGROUP ANALYSIS OF MAIA

Leukemia, 2022 April; 36(4):1066–77

AUTHORS: Facon T, Cook G, Usmani SZ, et al.
CENTRE FOR CORRESPONDENCE: University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France

BACKGROUND & AIM: In the phase 3 MAIA trial, the human monoclonal antibody daratumumab, in combination with lenalidomide and dexamethasone (D-Rd), significantly improved progression-free survival (PFS) and induced deeper responses than lenalidomide plus dexamethasone alone (Rd) in transplant-ineligible participants with newly diagnosed multiple myeloma (NDMM), including participants aged 75 years and older. However, people with NDMM have widely varying levels of fitness, and analysing a treatment according to participants' frailty can be more informative than using their age. The aim of this study was therefore to analyse the MAIA data across subgroups according to frailty.

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

ENDPOINTS: PFS; overall response rate; complete response or better; minimal residual disease negativity; treatment-emergent adverse events (TEAEs).

METHOD: In MAIA, participants were randomized to receive D-Rd (*n*=368) or Rd (*n*=369) until disease progression or unacceptable toxicity. A retrospective frailty assessment was performed using age, Charlson comorbidity index and baseline Eastern Cooperative Oncology Group performance status score to classify participants as fit, intermediate, non-frail (i.e. fit + intermediate) or frail.

RESULTS: Overall, 396 participants were non-frail (D-Rd, *n*=196; Rd, *n*=200) and 341 were frail (D-Rd, *n*=172; Rd, *n*=169). Over a median follow-up of 36.4 months, a PFS benefit for D-Rd versus Rd was observed in all frailty subgroups (table). The overall response rate with D-Rd versus Rd was 98.0% versus 84.5% ($p<0.0001$) in non-frail participants and 87.2% versus 78.1% ($p=0.0265$) in frail participants. Higher rates of complete response or better and minimal residual disease negativity (10^{-5} sensitivity threshold) were seen with D-Rd versus Rd across all frailty subgroups. With both D-Rd and Rd, the incidence of grade 3/4 TEAEs was higher in frail participants (94.6% and 89.2%, respectively) than non-frail participants (89.3% and 82.9%, respectively). The most common grade 3/4 TEAE with D-Rd and Rd was neutropenia (45.4% and 37.2% of non-frail participants; 57.7% and 33.1% of frail participants).

CONCLUSION: In transplant-ineligible people with NDMM, D-Rd showed greater efficacy than Rd across all frailty subgroups.

Median PFS among participants treated with D-Rd versus Rd by frailty subgroup

Frailty subgroup	Median PFS, months		Hazard ratio (95% confidence interval)	*p*-value
	D-Rd	Rd		
Fit	Not reached	41.7	0.41 (0.22–0.75)	0.0028
Intermediate	Not reached	Not reached	0.53 (0.35–0.80)	0.0024
Non-frail	Not reached	41.7	0.48 (0.34–0.68)	<0.0001
Frail	Not reached	30.4	0.62 (0.45–0.85)	0.003

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LONGITUDINAL MINIMAL RESIDUAL DISEASE ASSESSMENT IN MULTIPLE MYELOMA PATIENTS IN COMPLETE REMISSION –

RESULTS FROM THE NMSG FLOW-MRD SUBSTUDY WITHIN THE EMN02/HO95 MM TRIAL

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AUTHORS: Schmitz A, Brøndum RF, Johnsen HE, Mellqvist UH, Waage A, Gimsing P, Op Bruinink DH, van der Velden V, van der Holt B, Hansson M, Andersen NF, Frølund UC, Helleberg C, Schjesvold FH, Ahlberg L, Gulbrandsen N, Andreasson B, Lauri B, Haukas E, Bødker JS, Roug AS, Bøgsted M, Severinsen MT, Gregersen H, Abildgaard N, Sonneveld P, Dybkær K
CENTRE FOR CORRESPONDENCE: Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

BACKGROUND & AIM: Minimal residual disease (MRD) in multiple myeloma (MM) is the presence of a small number of residual myeloma cells after therapy. MRD is strongly associated with disease prognosis, but its role in guiding treatment decisions in MM is unclear. As part of the EMN02/HO95 trial, people with newly diagnosed MM underwent repeated bone marrow flow cytometry-based monitoring of MRD (flow-MRD), providing an opportunity to explore how MRD relates to disease progression. The aim of this study was to evaluate these longitudinal flow-MRD assessments in EMN02/HO95 participants who were in complete remission during maintenance therapy, and assess whether the development of MRD preceded changes in biochemical parameters of the disease.

STUDY DESIGN: Substudy of a phase 3 trial.

ENDPOINT: Development of MRD, assessed with flow-MRD.

METHOD: The analysis included 20 trial participants in complete remission during maintenance therapy who had at least three sequential bone marrow flow-MRD assessments. In individuals with increasing MRD, the timing of MRD positivity on flow-MRD was compared with the timing of changes in biochemical parameters (serum free light chain and M-component) and clinical progression. The minimum malignant plasma cells detection limit on flow-MRD was defined as $4x10^{-5}$.

RESULTS: Of the 20 individuals included in the analysis, 13 displayed sustained flow-MRD negativity accompanied by normal biochemical values. All of these participants remained free from clinical progression during 6 years of follow-up. One individual developed extramedullary disease without bone marrow involvement. The remaining six participants had increasing flow-MRD results. In these participants, flow-MRD positivity was observed at an average of 5.5 months before biochemical parameters became abnormal and 12.6 months before clinical progression was seen. The mean malignant plasma cell doubling time in these six participants was 1.8 months.

CONCLUSION: Among people with MM in complete remission, increasing levels of MRD assessed using flow-MRD preceded biochemical changes and were an early indication of subsequent clinical progression.

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SURVIVAL AFTER ACUTE EPISODES OF IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA (ITTP) – COGNITIVE FUNCTIONING AND HEALTH-RELATED QUALITY OF LIFE IMPACT:

A DESCRIPTIVE CROSS-SECTIONAL SURVEY OF ADULTS LIVING WITH ITTP IN THE UNITED KINGDOM

Hematology, 2021 December; 26(1):465–72

AUTHORS: Holmes S, Podger L, Bottomley C, Rzepa E, Bailey KM, Chandler F
CENTRES: Sanofi Genzyme, Reading; OPEN Health, Marlow, UK

BACKGROUND & AIM: Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a life-threatening thrombotic microangiopathy that can lead to thrombocytopenia, tissue ischaemia and organ dysfunction, and ultimately death if left untreated. People who survive acute episodes of iTTP are in danger of relapse, but the rarity of the condition means there is little information on their ongoing health-related quality of life (HRQoL) and other outcomes. The aim of this study was to better understand the burden of disease among people who have survived an acute episode of iTTP.

STUDY DESIGN: Online survey.

ENDPOINTS: HRQoL; cognitive function; work productivity.

METHOD: The study included 50 UK adults with a self-reported diagnosis of iTTP who were asked to complete an online survey (developed with a four-step process that included patient-engagement exercises). Patient-reported outcome measures incorporated into the survey included the Short Form-36 Version 2 (SF-36v2), Hospital Anxiety and Depression Score (HADS), PROMIS Cognitive Function Abilities Subset – Short Form 6a (PROMIS CFAS – SF6a) and Work Productivity and Activity Index: Specific Health Problem (WPAI-SHP). The survey also included several iTTP-specific questions. All data were analysed using descriptive statistics.

RESULTS: The study participants had a mean of 2.7 lifetime acute episodes of iTTP. Their mean standardized SF-36v2 physical and mental component scores were 42.16 and 33.61, respectively, compared with a mean of 50 for the US general population. The mean standardized PROMIS CFAS – SF6a score was 39.69 (also lower than the population norm), while the mean HADSs were 12.18 for anxiety and 11.78 for depression (both indicating moderate levels). Overall, 42.73% of participants who were employed at the time of completing the survey said that their illness had caused a loss of work productivity. Other consequences of iTTP reported by the participants included flashbacks; interference of fatigue in their family, social and intimate life; and fear of relapse. Participants who had their last episode of iTTP more than 12 months previously generally had better HRQoL and less activity impairment than those with a more recent episode.

CONCLUSION: People who had survived an acute episode of iTTP reported substantial impairments in HRQoL, cognitive function and work productivity.

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DARATUMUMAB, CARFILZOMIB, LENALIDOMIDE, AND DEXAMETHASONE WITH MINIMAL RESIDUAL DISEASE RESPONSE-ADAPTED THERAPY IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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AUTHORS: Costa LJ, Chhabra S, Medvedova E, Dholaria BR, Schmidt TM, Godby KN, Silbermann R, Dhakal B, Bal S, Giri S, D'Souza A, Hall A, Hardwick P, Omel J, Cornell RF, Hari P, Callander NS
CENTRE FOR CORRESPONDENCE: Division of Hematology and Oncology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

BACKGROUND & AIM: The presence of minimal residual disease (MRD) after initial therapy is the strongest prognostic factor in people with newly diagnosed multiple myeloma (NDMM). The aim of this study was to investigate whether using MRD to inform the use and duration of daratumumab, carfilzomib, lenalidomide and dexamethasone (Dara-KRd) consolidation treatment after autologous haematopoietic cell transplantation (AHCT) in people with NDMM can improve outcomes.

STUDY DESIGN: Multicentre, single-arm, phase 2 study.

ENDPOINTS: Primary: proportion of participants with MRD negativity. Secondary endpoints included progression-free and overall survival, and the cumulative incidence of progression or MRD resurgence in those managed with MRD surveillance.

METHOD: Adults with NDMM (*n*=123) received four cycles of Dara-KRd induction followed by AHCT and up to eight cycles of Dara-KRd consolidation, depending on their MRD status. The study population was enriched for participants with high-risk cytogenetic abnormalities (HRCAs; *n*=46 with one HRCA and *n*=24 with two or more HRCAs). MRD was evaluated using next-generation sequencing after induction, 60–80 days post-AHCT and after every four cycles of consolidation therapy. Participants with two consecutive MRD-negative assessments were moved to MRD surveillance, with MRD assessed after 6 and 18 months.

RESULTS: The median follow-up was 23.8 months. A total of 84 participants (71%) had two consecutive MRD-negative assessments and transitioned to MRD surveillance: 42 after AHCT, 33 after four cycles of Dara-KRd consolidation and nine after eight cycles. At the time of writing, the median follow-up after entering the surveillance period was 14.2 months. Six participants had disease progression during therapy; all participants with progression had gain/amplification of 1q, five had del(17p), and five had two or more HRCAs. For the whole population, the 2-year progression-free and overall survival rates were 87% and 94%, respectively. The cumulative incidence of MRD resurgence/progression 12 months after cessation of therapy was 4%, 0% and 27% for participants with zero, one, or two or more HRCAs, respectively. The most common serious adverse events were pneumonia (6%) and venous thromboembolism (3%).

CONCLUSION: Consolidation therapy adapted according to the individual's MRD response after Dara-KRd and AHCT led to high rates of MRD negativity in people with NDMM.

https://doi.org/10.1200/JCO.21.01935

Prescribing Information: SARCLISA (isatuximab) ▼ 20mg/mL concentrate for solution for infusion
Please refer to the Summary of Product Characteristics (SPC) before prescribing.

Presentations: Each vial contains 100 mg of isatuximab in 5 mL of concentrate or contains 500 mg of isatuximab in 25 mL of concentrate.
Indication: SARCLISA is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy. Sarclisa is indicated in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
Dosage and Administration: SARCLISA should be administered by a healthcare professional, in an environment where resuscitation facilities are available. *Premedication, with the following medicinal products, should be administered 15-60 minutes prior to starting a SARCLISA infusion:* Dexamethasone 40 mg oral or intravenous (IV) (or 20 mg oral or IV for patients ≥75 years of age) when administered in combination with isatuximab and pomalidomide; Dexamethasone 20 mg (IV on the days of isatuximab and/or carfilzomib infusions, and oral on the other days): when administered in combination with isatuximab and carfilzomib; Paracetamol 650 mg to 1000 mg oral (or equivalent); Diphenhydramine 25 mg to 50 mg IV or oral (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The IV route is preferred for diphenhydramine for at least the first 4 infusions. The above recommended dose of dexamethasone (oral or IV) corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide and before isatuximab and carfilzomib administration. Patients who do not experience an infusion reaction upon their first 4 administrations of SARCLISA may have their need for subsequent premedication reconsidered. *Managing neutropenia:* The use of colony-stimulating factors (e.g. G-CSF) should be considered to mitigate the risk of neutropenia. In the event of grade 4 neutropenia, SARCLISA administration should be delayed until neutrophil count improves to at least 1.0 x 10^9/L. *Posology:* The recommended dose of SARCLISA is 10 mg/kg body weight administered as an IV infusion in combination with pomalidomide and dexamethasone (Isa-Pd regimen) or in combination with carfilzomib and dexamethasone (Isa-Kd regimen). *Cycle 1:* Dosing on days 1, 8, 15 and 22 (weekly). *Cycle 2 and beyond:* Dosing on days 1, 15 (every 2 weeks). Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity. For other medicinal products that are administered with SARCLISA, refer to the respective current summary of product characteristics. The administration schedule must be carefully followed. *Missed dose:* If a dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval. *Dose adjustments:* No dose reduction of SARCLISA is recommended. Administration adjustments should be made if patients experience infusion reactions. *Infusion rates:* please refer to full SmPC.
Special Populations: *Elderly:* no dose adjustment is recommended. *Patients with mild to severe renal impairment:* no dose adjustment is recommended. *Patients with mild hepatic impairment:* no dose adjustment is recommended. Data in patients with moderate and severe hepatic impairment are limited, but there is no evidence to suggest that dose adjustment is required in these patients. *Paediatric population (<18 years old):* No data available.
Contraindications: Hypersensitivity to the active substance or to any of its excipients.
Precautions and Warnings: *Traceability:* In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. *Infusion reactions:* Infusion reactions, mostly mild or moderate, have been observed in 38.2% of patients treated with SARCLISA in ICARIA-MM (Isa-Pd regimen), and in 45.8% of patients in the IKEMA trial (Isa-Kd regimen). In ICARIA-MM, all infusion reactions started during the first SARCLISA infusion and resolved on the same day in 98% of the infusions. The most common symptoms of an infusion reaction included dyspnoea, cough, chills and nausea. The most common severe signs and symptoms included hypertension, dyspnoea and bronchospasm. In IKEMA, the infusion reactions occurred on the infusion day in 99.2% of episodes. In 94.4% of those experiencing an infusion reaction experienced it during the first cycle of treatment. All infusion reactions resolved. The most common symptoms of an infusion reaction included cough, dyspnoea, nasal congestion, vomiting and nausea. The most common severe signs and symptoms included hypertension and dyspnoea. Serious infusion reactions including severe anaphylactic reactions have been observed after SARCLISA administration. Vital signs should be frequently monitored during the entire SARCLISA infusion. When required, interrupt SARCLISA infusion and provide appropriate medical and supportive measures. In case symptoms do not improve after interruption of SARCLISA infusion, persist or worsen despite appropriate treatment with medicinal products, require hospitalization or are life-threatening, permanently discontinue SARCLISA and institute appropriate management. *Neutropenia:* In patients receiving Isa-Pd, neutropenia occurred as a laboratory abnormality in 96.1% of patients and as an adverse reaction in 46.7% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 84.9% of patients and as an adverse reaction in 45.4% of patients. Neutropenic complications have been observed in 30.3% of patients, including 11.8% of febrile neutropenia and 25.0% of neutropenic infections. In patients treated with Isa-Kd, neutropenia occurred as a laboratory abnormality in 54.8% of patients and as an adverse reaction in 4.5% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 19.2% of patients (with 17.5% Grade 3 and 1.7% Grade 4) and as an adverse reaction in 4.0% of patients. Neutropenic complications have been observed in 2.8% of patients, including 1.1% of febrile neutropenia and 1.7% of neutropenic infections. Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored for signs of infection. *Infection:* A higher incidence of infections including grade ≥3 infections, mainly pneumonia, upper respiratory tract infection and bronchitis, occurred with SARCLISA. Patients receiving SARCLISA should be closely monitored for signs of infection and appropriate standard therapy instituted. Antibiotics and antiviral prophylaxis can be considered during treatment. *Second primary malignancies (SPMs):* In ICARIA-MM, SPMs were reported in 6 patients (3.9%) treated with Isa-Pd and in 1 patient (0.7%) treated with Pd, and included skin cancer in 4 patients treated with Isa-Pd and in 1 patient treated with Pd. Patients continued treatment after resection of the skin cancer. In IKEMA, SPMs were reported in 13 patients (7.3%) treated with Isa-Kd and in 6 patients (4.9%) treated with Kd. SPMs were skin cancers in 9 patients (5.1%) treated with Isa-Kd and in 3 patients (2.5%) treated with Kd, and were solid tumours other than skin cancer in 5 patients (2.8%) treated with Isa-Kd and in 4 patients (3.3%) treated with Kd. One patient (0.6%) in the Isa-Kd group and one patient (0.8%) in the Kd group had both skin cancer and solid tumours other than skin cancer. Patients with skin cancer continued treatment after resection of the skin cancer. Solid tumours other than skin cancer were diagnosed within 3 months after treatment initiation in 3 patients (1.7%) treated with Isa-Kd and in 2 patients (1.6%) treated with Kd. The overall incidence of SPMs in all the SARCLISA-exposed patients is 3.6%. Physicians should carefully evaluate patients before and during treatment as per IMWG guidelines for occurrence of SPM and initiate treatment as indicated. *Interference with Serological Testing (indirect antiglobulin test):* SARCLISA administration may result in a false positive indirect antiglobulin test (indirect Coombs test). To avoid potential problems with Red Blood Cell transfusion, patients being treated with SARCLISA should have blood type and screen tests performed prior to the first SARCLISA infusion. Phenotyping may be considered prior to starting SARCLISA treatment as per local practice. If treatment with SARCLISA has already started, the blood bank should be informed that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol (DTT)-treated RBCs. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices. *Interference with determination of complete response:* SARCLISA can interfere with both serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. Interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein. ***Interactions:*** *Interference with serological testing:* Because CD38 protein is expressed on the surface of red blood cells, SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with potential false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with SARCLISA. *Interference with Serum Protein Electrophoresis and Immunofixation Tests:* SARCLISA may be incidentally detected by serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the monitoring of M-protein and could interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria. *Fertility, pregnancy and lactation:* Women of childbearing potential treated with SARCLISA should use effective contraception during treatment and for at least 5 months after cessation of treatment. There are no available data on isatuximab use in pregnant women. Immunoglobulin G1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. The use of SARCLISA in pregnant women is not recommended. It is unknown whether isatuximab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; however, a risk to the breast-fed infant cannot be excluded during this short period just after birth. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from isatuximab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. No human and animal data are available to determine potential effects of isatuximab on fertility in males and females.
Adverse Reactions: In ICARIA-MM (Isa-Pd): *Very common:* Neutropenia, infusion reactions, pneumonia*, upper respiratory tract infection, diarrhoea, bronchitis, dyspnoea, nausea, febrile neutropenia*, vomiting. *Common:* Decreased appetite, weight decreased, atrial fibrillation, skin squamous cell carcinoma. In IKEMA (Isa-Kd): *Very common:* Infusion reactions, hypertension, diarrhoea, upper respiratory tract infection, pneumonia*, fatigue, dyspnoea, insomnia, bronchitis, back pain, cough and vomiting. *Common:* Skin cancers, neutropenia, solid tumours other than skin cancers. *Uncommon:* Anaphylactic reaction*. *These adverse events also occurred as serious adverse events.
Prescribers should consult the SPC in relation to other adverse reactions.
Marketing Authorisation Holder: Sanofi-aventis groupe, 54 rue La Boétie, 75008 Paris, France.
Date of last revision of SmPC: June 2022

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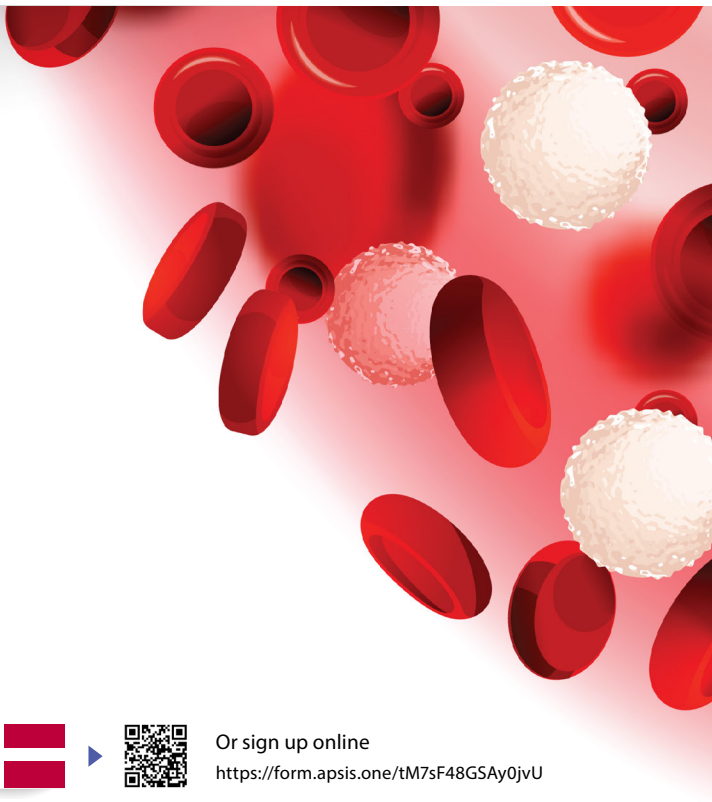

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