REVIEW ARTICLE

Functional cure and long-term survival in multiple myeloma: how to challenge the previously impossible

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Abstract

Multiple myeloma (MM) is a heterogeneous disease with survival ranging from months to decades. The goal of 'cure' remains elusive for most patients, but has been shown to be possible, with durable remission and a transition to a plateau phase (analogous to monoclonal gammopathy of uncertain significance/smoldering myeloma). In this review, two representative cases set the stage to illustrate how this might be possible and what still needs to be determined to achieve functional disease control over a prolonged period. Several developments have emerged, such as improved diagnostics including the definitions and use of SLiM-CRAB criteria and measurable residual disease (MRD) with whole-genome/single-cell sequencing as well as other correlates to better understand disease biology. These advances enable earlier detection, more accurate risk stratification and improved personalized treatment strategies by facilitating analysis of genetic alterations and clonal heterogeneity. Whole-genome sequencing may also identify driver mutations and modes of resistance to immunotherapies as well as other targeted therapies. Today, induction with a CD38 antibody, proteasome inhibitor, immunomodulatory drug, and dexamethasone, potentially followed by autologous stem cell transplantation and lenalidomide maintenance, can be considered standard of care for transplant-eligible (TE) patients with newly diagnosed MM (NDMM). That prolonged disease control and functional cure can be achieved in non-transplant-eligible (NTE) patients is currently emerging as a distinct possibility: data from phase III trials that incorporate a CD38 antibody into the treatment of NTE NDMM patients demonstrate impressive MRD negativity rates that appear sustained over several years. While the long-term durability of chimeric antigen receptor T cells, bi-specific antibodies and other immunotherapies are being evaluated, several clinical trials are now investigating their role in frontline treatment for TE and NTE patients. These trials will address whether chimeric antigen receptor T-cell therapy will replace autologous stem cell transplantation and whether such immunotherapies will represent a truly curative option. We conclude that while cure remains elusive, the concept of operational or functional cure provides a new benchmark to strive for and is an emerging area of active and potentially achievable clinical research for MM.

Introduction

Multiple myeloma (MM) is a complex and heterogeneous disease with survival ranging from months to decades from primary diagnosis based on a patient's risk profile.[1] However, the ultimate goal of achieving "cure" remains elusive for almost all patients. Use of the term "cure" for some cancer entities is being debated in view of the increasing survival rates in various cancers and the development of survivorship care as an essential component of hematology/oncology. Some hematologists/oncologists prefer to use "long-term survivor" instead of "cured patient" and although patients prefer "cured", practitioners may consider this as impossible in some settings. From conditional survival analyses, it has been shown that the risk of death from cancer is highest in the initial years after diagnosis, decreases progressively, until a time at which the risk becomes negligible, and surviving patients reach a life expectancy that may

match the sex- and age-matched general population.[2-4] Thus, conditional survival is defined as the probability of a patient surviving an additional 5 (or 10) years after already surviving a given number of years.[2-4] Nowadays, patients with various cancers are expected to have increasing survival as a result of personalized treatments based on better understanding of the biology and potential response to more effective therapies. Therefore: (i) cancer patients can be defined as "cured", when their life expectancy is the same as that of the sex- and age-matched general population; (ii) the biological characterization of a tumor and its site, stage, and disease-free interval are variables that influence the correct applicability of the word "cured"; and (iii) considering the social implications of cancer, the word "cured" in certain societies and cultural contexts could also facilitate the return of cancer patients to their personal and professional life after cancer by reducing the risk of work and insurance discrimination.[5] This article will provide an overview of the current landscape of MM treatment, the concept of achieving cure in MM, and the historical perspectives that have shaped our understanding of MM treatment to date.

Data collection and methods

The panel of authors reviewed available published evidence from randomized clinical studies, meta-analyses, systematic reviews, observational studies, meetings and case reports. The Medline, Embase and Cochrane bibliographic databases were searched from manuscript conception to June 12, 2023. Potentially eligible studies written in English were sought with a combination of search terms (*Online Supplementary Figure S1*). Search terms were "multiple myeloma", "cure", "operational cure", "minimal residual disease" and "long-term remission". To estimate frequencies of patients attaining 'cure' or 'operational cure', the outpatient clinic of the University of Freiburg (UKF) was methodically assessed as described in Table 1A and B. Long-term remission or "cure" was defined as a stringent complete response maintained for 5 years or more, with no antimyeloma therapy, no symptoms and good quality of life. Likewise, "operational cure" was assessed for/assigned to those patients in smoldering MM states for 5 or more years, asymptomatic with no CRAB symptoms (hypercalcemia, renal insufficiency, anemia, bone lesions), but immunofixation-positive, without anti-MM treatment and with a good quality of life (Table 1B). The term "smoldering MM" refers to the definitions in European Myeloma Network (EMN) papers,[6,7] in which, after successful treatment, transformation from active myeloma to smoldering or almost non-existent myeloma, but with detection of the disease, was described. Representative patients were selected as case examples of cure and operational cure (Table 2). Moreover, due to the longer than 1.5-year endpoint during discussion between the four authors of this review regarding MM patients who are "cured" or in "long-term remission", this concept is being assessed (not only via conditional survival analyses[2-4]), but also in, for example, the ALCYONE, MAIA and CASSIOPEIA studies. If our definitions of "cured" and "long-term remission" are applied to MM patients, true plateaus do occur (*personal communication*). We therefore consider this review of a few patients who are truly cured or remain in long-term remission of value in order to advance these and subsequent analyses.
The draft of this paper was generated between January 2022 and June 2023 during the course of 3-monthly meetings of the authors as representatives of the German Multiple Myeloma study groups (DSMM/GMMG), the EMN and the International Myeloma Working Group (IMWG).

Case presentation – towards functional cure

A 46-year-old woman was diagnosed with MM in June 2004. At the time of diagnosis, she had an IgG (32 g/L) lambda subtype (λ-serum free light chains: 400 mg/L), International Staging System (ISS)/Revised International Staging System (R-ISS) score of I, standard-risk cytogenetics and bone marrow infiltration by monoclonal plasma cells of 10%. Imaging (whole-body computed tomography) showed a large extramedullary mass in the pelvis, with the largest diameter measuring 7 cm. The woman's Revised-Myeloma Comorbidity Index score[8-10] was 2/9, indicating that she was fit for intensive treatment. Due to the large extramedullary myeloma lesion in the pelvis, the bone marrow plasma cell infiltrate of 10%, positive immunofixation, and elevated IgG and λ-serum free light chains at initial diagnosis, we had excluded the diagnosis of 'solitary plasmacytoma of the pelvis and high-dose local radiotherapy as local treatment'. We thoroughly discussed this patient with the directors of the GMMG/DSMM study groups (Profs. Drs. Goldschmidt and Einsele) and, given the non-solitary nature of this IgGλ-MM, had decided for systemic treatment. In 2004, the patient was enrolled in the DSMM-V study,[11] given chemotherapy-based induction therapy (idarubicin-dexamethasone), and underwent stem cell mobilization and subsequent tandem autologous stem cell transplantation (ASCT). The patient did not receive any novel agents during induction, consolidation or maintenance. The treatment was successful and the patient achieved a stringent complete remission by February 2005 and has remained in stringent complete remission for over 16 years since achieving this milestone. The patient's risk factors for MM recurrence were relatively low. She had a standard-risk cytogenetic profile, ISS/R-ISS both I and a low bone marrow infiltration. The patient's age of 46 years at the time of diagnosis was also favorable. Additionally, the patient's large extramedullary mass in the pelvis was successfully treated with the ASCT. Althought we cannot completely exclude that a similarly favorable result would have been achieved with high-dose radiation, the bone

Table 1A. Examples and characteristics of patients with multiple myeloma who achieved long-term remission and cure* (University of Freiburg, UKF).

Case	Age at ID in years	Sex	Date of ID of MM	Risks (ISS, CC, BM, RI, R-MCI)	MM therapy	ASCT	Maintenance	Remission duration
1	46	Female	6/2004	IgGλ, ISS/R-ISS I, SR, 10%, large EM MM pelvis (7 cm), no RI, R-MCI: 2/9=fit	R→DSMMV+Tandem-Tx	Yes: Tandem Mel200	No	sCR since 2/2005 = +18 years
2	45	Male	10/2009	IgAλ, ISS/R-ISS I, SR, 20%, no RI, R-MCI: 2/9=fit	DSMMXII: RAD, CE+Tandem-Tx	Yes: Tandem Mel200	Yes: R	sCR since 6/2010 = +13 years
3	52	Female	12/2010	IgGκ, ISS/R-ISS II, SR, 80%, no RI, R-MCI: 2/9=fit	VCD, IEV, Tx	Yes: Mel200	No	sCR since 9/2011 = +12 years
4	46	Male	4/2012	IgGκ, ISS/R-ISS I, SR, 30%, no RI, R-MCI: 4/9=intermediate.	VCD, EVC, Tx	Yes: Mel200	No	sCR since 9/2012 = +11 years
5	74	Female	6/2017	κ-LC, ISS/R-ISS I, unfavorable (1q, del20p), 40%, no RI, R-MCI: 5/9=intermediate.	VRd, CE, Tx	Yes: Mel140	Yes: Vd	sCR since 6/2018 = +5 years
Summary and median/ mean (range)	46/52 (45-74)	Females: 3, Males: 2	2004-2017	ISS/R-ISS I: 4, II: 5, SR: 4, BM: 30/40 (10-80), No RI: 5, R-MCI: 2/3 (2-5)	Tx: 5	Tandem-Tx: 2	Maintenance: 2	12/12 years (5-18)

*Definition of 'cure': stringent complete remission for ≥5 years, no therapy, no symptoms or SLiM-CRAB criteria, immunofixation (serum and urine) negative, good quality of life. Frequency determined from a search of outpatient clinics at the University of Freiburg between 1.1.2023-31.3.2023 in which 190 patients with multiple myeloma were identified, of whom five were potentially cured (5/190=2.6%). ID: initial diagnosis; MM: multiple myeloma; ISS: International Staging System; CC: cytogenetics (fluorescence *in situ* hybridization); BM: bone marrow infiltration of plasma cells; RI: renal impairment; R-MCI: Revised Myeloma Comorbidity Index; ASCT: autologous stem cell transplantation; EM: extramedullary site of MM lesion; R-ISS: Revised International Staging System; SR: standard risk; R: lenalidomide; DSMM: German MM study group Würzburg; DSMMV: idarubicin-dexamethasone induction with tandem-transplantation in transplant-eligible patients with newly diagnosed MM; Tx: autologous stem cell transplantation; Mel200: conditioning with melphalan 200 mg/m^2; sCR: stringent complete remission; RAD: lenalidomide, adriamycin, dexamethasone; LC: light chain; CE: cyclophosphamide, etoposide; VCD: bortezomib, cyclophosphamide, dexamethasone; IEV/EVC: ifosfamide, epirubicin, etoposide; VRd: bortezomib, lenalidomide, dexamethasone; Mel140: conditioning with melphalan 140 mg/m^2; +: ongoing.

marrow infiltration and well-secreting IgGλ-nature of her disease did seem to exclude this. While the definition of cure in MM is still debated, this patient's prolonged remission is a strong indication that she may have achieved a functional cure from her disease. Other selected and represented patients in long-term remission are summarized in Table 1A.

Case presentation – long-term disease control

While the sustained absence of any kind of measurable disease activity is a pre-requisite for curing MM, some patients experience persistence of a very low level of detectable MM cells while either on or off treatment but remain in deep response for even decades. Disease activity in such patients resembles monoclonal gammopathy of undetermined significance or low-risk smoldering MM rather than overt MM requiring therapy, and is sometimes referred to as a plateau phase. The term 'operational or functional cure' has been introduced to describe such monoclonal gammopathy of undetermined significance- or smoldering MM-like behavior after successful induction therapy.[12] Definitions and typical features of cure, operational cure and incurable MM are displayed in Table 2.

The following history of a 52-year-old male who was diagnosed with MM in June 2003 represents a classical case of an operational cure. His clinical characteristics included an IgG kappa (κ) subtype (IgG 60 g/L, κ-serum free light chains: 650 mg/L), an ISS/R-ISS score of I, and standard-risk cytogenetics. The initial bone marrow biopsy revealed an infiltration rate of 50%. There was no prevalent

Table 1B. Examples and characteristics of patients with multiple myeloma who achieved a state of smoldering disease (University of Freiburg, UKF).

Case	Age at ID in years	Sex	Date of ID of MM	Risks (ISS, CC, BM, RI, R-MCI)	MM therapy	ASCT	Maintenance	Remission duration
1	52	Male	6/2003	IgGκ, ISS/R-ISS I, SR, 50%, no RI, R-MCI: 2/9=fit	DSMMV, IEV+Tandem-Tx	Yes: Tandem-Mel200	No	VGPR; SMM since 2/2004 = +19 years
2	65	Male	6/2010	IgGκ, ISS/R-ISS I, SR, 20%, no RI, R-MCI: 3/9=fit	DSMMXII: RAD, CE+Tandem-Tx	Yes: Tandem-Mel200	Yes: R	VGPR; SMM since 4/2011 = +12 years
3	49	Female	4/2018	κ-LC, ISS/R-ISS II, SR, 70%, RI, R-MCI: 3/9=fit	VCD, C, Tx	Yes: Mel140	Yes: Vd	VGPR; SMM since 9/2018 = +5 years
4	71	Female	7/2014	κ-LC, ISS/R-ISS III/II, unfavorable, 20%, RI, R-MCI: 5/9=intermediate	VCD, CE, Tx	Yes: Mel140	Yes: Vd	VGPR; SMM since 11/2014 = +8 years
5	56	Male	6/2017	IgGκ, ISS/R-ISS II, unfavorable (del1p, del16q), 90%, RI, R-MCI: 3/9=fit.	VCD, CE, Tx	Yes: Mel200	Yes: Vd	VGPR; SMM since 8/2017 = +6 years
6	45	Male	2/2008	IgAλ, ISS/R-ISS I, SR, 20%, no RI, R-MCI: 5/9=intermediate.	DSMMXI: VCD, IEV, Tx	Yes: Tandem-Mel200	Yes: R	VGPR; SMM since 12/2014 = +8 years
7	41	Female	6/2008	IgGλ, ISS/R-ISS I, SR, 40%, no RI, R-MCI: 2/9, SPM (BC→CR)	DSMMXI: VCD, IEV, Tx	Yes: Tandem-Mel200	Yes: R	VGPR; SMM since 12/2014 = +8 years
Summary and median/ mean (range)	52/54 (42-71)	Females: 3, Males: 4	2003-2018	ISS/R-ISS I: 4, II: 3, SR: 5, BM: 40/40 (20-90), No RI: 4, R-MCI: 3/3 (2-5)	Tx: 7	Tandem-Tx: 4	Maintenance: 6	8/9 (5-19)

*Definition of smoldering multiple myeloma: transformation to smoldering state ≥5 years, very good partial remission (VGPR), no therapy, no symptoms or SLiM-CRAB criteria, immunofixation (serum and urine) positive, good quality of life. Frequency determined from a search of outpatient clinics at the University of Freiburg between 1.1.2023-31.3.2023 in which 190 patients with multiple myeloma were identified, of whom seven were in long-term VGPR (7/190=3.7%). ID: initial diagnosis; MM: multiple myeloma; ISS: International Staging System; CC: cytogenetics (fluorescence *in situ* hybridization); BM: bone marrow infiltration of plasma cells; RI: renal impairment; R-MCI: Revised Myeloma Comorbidity Index; ASCT: autologous stem cell transplantation; EM: extramedullary site of MM lesion; R-ISS: Revised International Staging System; SR: standard risk; DSMM: German MM study group Würzburg; DSMMV: idarubicin-dexamethasone induction with tandem-transplantation in transplant-eligible patients with newly diagnosed MM; IEV: ifosfamide, epirubicin, etoposide; Tx: autologous stem cell transplantation; Mel200: conditioning with melphalan 200 mg/m^2; SMM: smoldering multiple myeloma; RAD: lenalidomide, adriamycin, dexamethasone; CE: cyclophosphamide, etoposide; R: lenalidomide; LC: light chain; VCD: bortezomib, cyclophosphamide, dexamethasone; C: cyclophosphamide; Vd: bortezomib, dexamethasone; Mel140: conditioning with melphalan 140 mg/m^2; SPM: second primary malignancy; BC: breast cancer; CR: complete response/remission; + : ongoing follow-up.

renal impairment. The patient's Revised-Myeloma Comorbidity Index score was 2/9, indicating that he was fit to undergo ASCT. He was enrolled in the DSMM-V study and received tandem ASCT without maintenance therapy. Ever since completion of the second ASCT, residual monoclonal protein in the serum, indicative of disease activity, could be detected. Nevertheless, the patient has been in long-term remission with no evidence of disease progression. In this case, the patient has been in a state of sustained very good partial response for 20 years since his initial diagnosis. While the patient has low, detectable levels of monoclonal protein, he does not have any clinical symptoms or end-organ damage. Other representative patients with an 'operational or functional cure' are summarized in Table 1B.

Both cases demonstrate that even in the era before novel agents and molecular diagnostics, functional cure could be achieved for a very limited subset of patients. In our review, we summarize the changes in diagnostics and treatment of patients with MM in the last two decades that support the thesis that in the relatively near future, we will or are already achieving a higher proportion of

Table 2. Definitions of cure and functional cure and transformation in smoldering multiple myeloma.

Relevant parameters	Cure >5-10 years	'Operational cure'	Incurable
Definition	Considered less often (<10%), Sustained BM MRD-negative (NGS, NGF 10^{-5} – 10^{-6} levels) and imaging-negative (MRI, PET) for at least 1 year	In younger patients, receiving most active 3-4 agent therapy (PI+IMiD+CD38ab), in combination with ASCT, followed by maintenance In older patients receiving CD38ab-based therapies and novel immunotherapies Minimal levels of MRD remain positive	Considered typical for most (>90%) MM patients
Patient constitution	Fit patients	Younger and older patients	Frail patients
Cytogenetics and disease stages	Standard risk ISS I/II rather than ISS/R-ISS III	Both ISS/R-ISS: I-III	High-risk cytogenetics, especially del(17p) ISS/R-ISS: III
Stages of MM disease when therapy is initiated	Treat at an earlier stage: SLiM-CRAB + high-risk SMM states	Treat when SLiM-CRAB criteria present	Treat when severe and multiple CRAB symptoms (i.e. 4/4) present, dense BM infiltration and unresolving organ impairment
Therapy modalities	ASCT, tandem-ASCT, allo-SCT, possibly CAR T cells + BITE	ASCT + novel agent therapies	Unable to endure multiagent MM therapy
Lines of therapy	More likely to be achieved with first-line than with later-line treatment	With first-line and later relapse?	With successive relapses
Obtained response	Achievement of sustained CR, IF-negative, MRD-negative	CR and VGPR, MRD may remain positive	Only achievement of SD or PD or entirely non-responsive MM
Symptom evolution and QoL	Sustained relief of MM symptoms and improved QoL	Improved or stable MM symptoms and stable QoL	No relief of MM symptoms and worsening QoL

MM: multiple myeloma; QoL: quality of life; BM: bone marrow; MRD: measurable residual disease; NGS/NGF: next generation sequencing/flow; MRI: magnetic resonance imaging; PET-CT: positron emission tomography-computed tomography; ISS: International Staging System; R-ISS: Revised International Staging System; SLiM-CRAB: ≥60% bone marrow plasma cell infiltration, serum free light chain ratio ≥100, >1 MRI-defined focal lesion, hypercalcemia, renal impairment, anemia, bone lesions; SMM: smoldering multiple myeloma; ASCT: autologous stem cell transplantation; allo-SCT: allogeneic stem cell transplantation; CAR: chimeric antigen receptor; BITE: bispecific antibodies; CR: complete response; IF: immunofixation; PI: proteasome inhibitor; IMiD: immunomodulatory drugs; CD38ab: CD38-antibody; VGPR: very good partial response; SD: stable disease; PD: progressive disease.

deeper and durable long-term disease control in patients with newly diagnosed MM (NDMM) patients.

Historical perspectives

The history of MM diagnostics and treatment dates back to the 19th century, when the condition was first described by Henry Bence Jones in the 1850s as a distinct entity characterized by the presence of abnormal proteins in urine.[13] Despite the early discovery of monoclonal proteins in patients with bone destruction, hypercalcemia, anemia and renal insufficiency, MM remained a uniformly fatal disease with very limited treatment options until the late 1960s and early 1970s.

In the early days of MM treatment, the goal was primarily palliative, focused on managing symptoms such as bone pain and hypercalcemia. The only available treatments at the time were radiation therapy and high-dose corticosteroids, which provided temporary relief but failed to improve overall survival. In the 1960s, the introduction of combination therapy with melphalan and prednisone was the start of a new era of MM treatment.[14] This regimen provided more durable responses and improved survival, making melphalan and prednisone the standard of care for decades.

Despite these advances, the goal of MM treatment remained focused on symptom control, but provided little hope of achieving cure. However, the development of novel agents in the 1990s and 2000s marked a turning point in MM treatment. Thalidomide, a drug with anti-angiogenic properties, was found to induce responses in heavily pretreated MM patients,[15] leading to its approval in 1998. This was followed by the development of bortezomib and lenalidomide, which further expanded treatment options for MM patients. With the advent of these first-generation novel therapies, the goal of MM treatment shifted from palliation to symptom control to an increasing focus on achieving much deeper responses and prolonging survival. The earlier introduction of high-dose therapy and ASCT in the 1980s and 1990s also contributed to this shift in treatment goals.[16] ASCT was found to improve response rates and prolong survival in selected patients, and

it became a standard part of MM treatment for many years in younger patients, although its role is now rapidly evolving, with the option of delayed ASCT being preferred as well as even deferred in selected patients.

However, the ultimate goal of achieving cure remained elusive. Despite significant progress in MM treatment, only a small percentage of patients achieve long-term disease-free survival.[17] This led to the development of new treatment strategies aimed at achieving deeper and more durable responses. The concept of measurable residual disease (MRD) negativity emerged as a key goal of MM treatment, with studies showing that patients who achieved MRD negativity had improved outcomes (Figure 1).[18] Thus, there are rare cases of MM patients who are cured or in long-term remission, with the incidence rates being lower than those for patients with prostate, breast or colorectal cancer.[5] Although cure and/or long-term remission occurs less frequently for MM than for other cancers, it remains important to detect via conditional survival analyses or definitions as introduced here. Since Germany (and other countries worldwide) is suffering from "post-COVID" conditions, "release of hospital capacities" – as described in the last part of our review – is gaining ever more attention in our society. Thus, alongside patients' personal interest, there has been a growing general interest in the concept of operational cure in MM in recent years. This refers to patients who have achieved a durable remission without ongoing therapy, even if they may still have residual disease. While true cure may remain rare, the concept of operational cure provides a new benchmark for MM treatment and is an area of active research (Tables 1 and 2).

Advances in diagnosis and prognosis

Advances in diagnosis and prognosis have brought about significant improvements for early detection and prognostication in MM, increasing the chances of achieving potential long-term disease control and/or functional cure.

Changes in diagnostic criteria and prognostic indicators

Several developments have emerged, including changes in diagnostic criteria such as the introduction of the SLiM-CRAB criteria,[19] integration of prognostic indicators like MRD assessment,[20] whole-genome sequencing, and novel single-cell sequencing techniques to study the underlying disease biology.[21,22] These advances have revolutionized the field by enabling earlier detection, more accurate risk stratification, and personalized treatment strategies, ultimately enhancing the prospects of achieving long-term remission and potentially curing MM (Table 2).

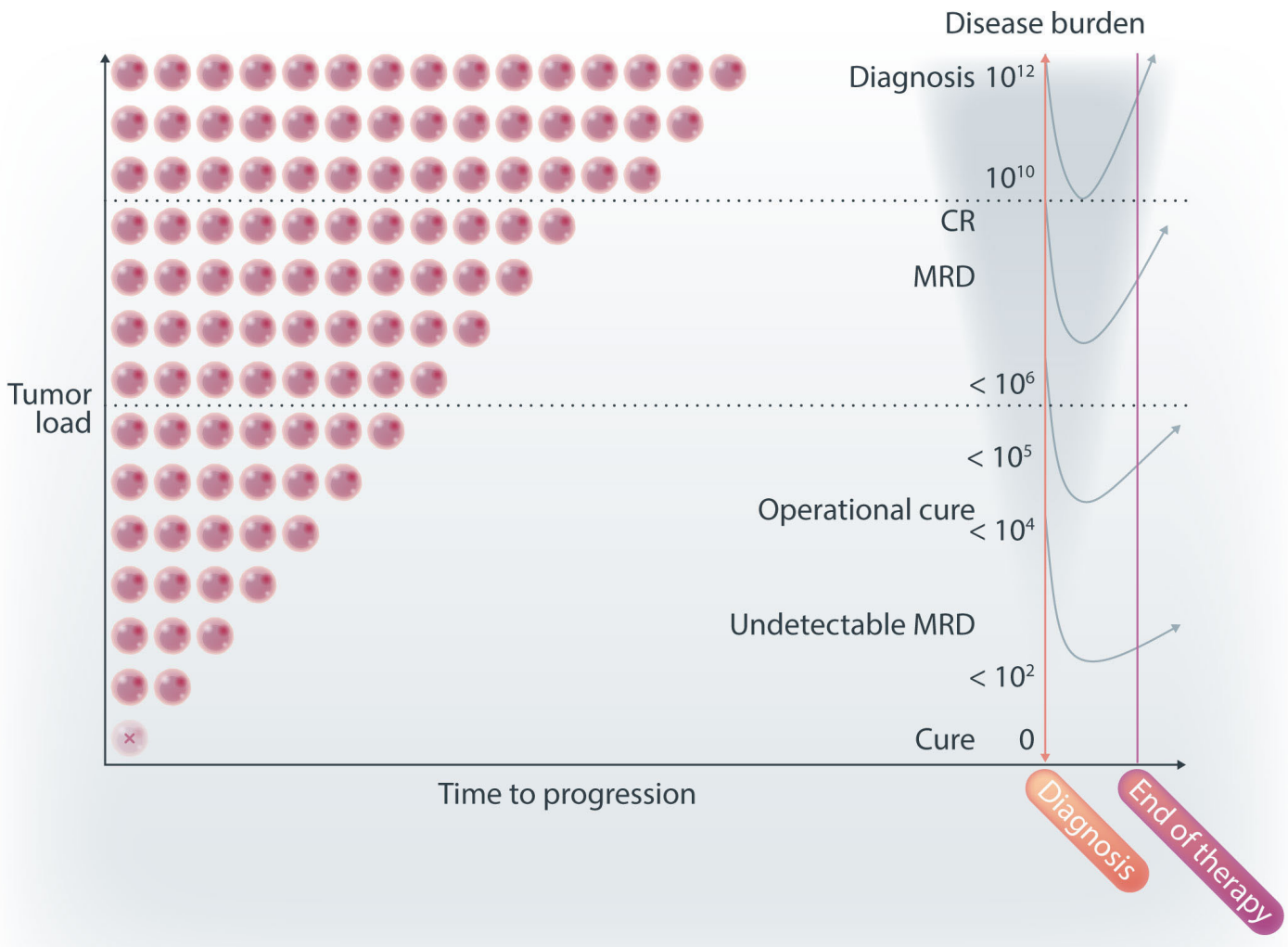

Figure 1. Correlation of depth of response and survival. CR: complete remission; MRD: measurable residual disease.

Table 3. Selected, phase III trials of those in which multiple myeloma treatment was adapted according to measurable residual disease.

Trial	N of pts	Primary endpoint	Treatment	MRD assessment + sensitivity	Treatment modification	Treatment restarting upon MRD positivity
MIDAS (NCT-4934475)	716	MRD negativity after consolidation	Isa-KRd induction and then randomization based on MRD	NGS (clonoSEQ) 10^{-5}	ASCT *vs.* not upon MRD achievement	N/A
PERSEUS (NCT-3710603)	690	PFS	VRd *vs.* D-VRd + ASCT, Rm *vs.* DRm	NGS (clonoSEQ) 10^{-5}	MRD-negative pts to stop daratumumab after sustained MRD-negativity	Daratumumab restarted at recurrence of MRD
AURIGA (NCT-3901963)	214	MRD conversion at 12 months	DRm *vs.* Rm after ASCT	NGS (clonoSEQ) 10^{-5}	>VGPR + MRD-positivity essential for study entry	N/A
DRAMMATIC (NCT-4071457)	1,100	OS	DRm *vs.* Rm after ASCT	NGS (clonoSEQ) 10^{-5}	Each arm (DR + R) randomly assigned to continuous *vs.* MRD-driven cessation of maintenance in MRD-negative pts	N/A
OPTIMUM (NCT-3941860)	510	OS, change in FACT TOI score	Rm+Ixa *vs.* R-placebo after ASCT	NGS (clonoSEQ) 10^{-5}	Must have MRD-positive disease prior to Rm	MRD-positive pts randomly assigned to Rm+Ixa or Rm+placebo
University Michigan (NCT-4140162)	50	MRD negativity after induction	DRd → D-VRd consolidation (only in MRD$^+$) → DRm → Rm	NGS (clonoSEQ) 10^{-5}	D-VRd consolidation in MRD-positive pts	N/A
MASTER (NCT-3224507)	123	MRD negativity after consolidation	D-KRd → ASCT → D-KRd consolidation (0-8 cycles depending on MRD) →Rm	NGS (clonoSEQ) 10^{-5}	Treatment stop after 2 consecutive MRD-negative evaluations	Daratumumab restarted at recurrence of MRD

Pts: patients; MRD: measurable residual disease; isa: isatuximab; KRd: carfilzomab, lenalidomide, dexamethasone; NGS: next-generation sequencing; ASCT: autologous stem cell transplantation; N/A: not applicable; PFS: progression-free survival; VRd: bortezomib, lenalidomide, dexamethasone; D-VRd: daratumumab, bortezomib, lenalidomide, dexamethasone; Rm: lenalidomide maintenance; DRm: daratumumab-lenalidomide maintenance; VGPR: very good partial remission; OS: overall survival; DR: daratumumab-lenalidomide; R: lenalidomide, FACT TOI: Functional Assessment of Cancer Therapy Trial Outcome Index; Rm+Ixa: lenalidomide-ixazomib maintenance. Adapted from: Mateos, Nooka, Larson. Am Soc Clin Oncol Educ Book. 2022:42:1-1292.

One notable advancement in the diagnosis of MM was the introduction of the SLiM-CRAB criteria by the IMWG in 2014. The traditional CRAB criteria, which include hypercalcemia, renal insufficiency, anemia and bone lesions, were initially used to identify patients with active disease requiring treatment. However, they often failed to capture early-stage myeloma or rapidly evolving disease, which could delay the initiation of appropriate therapy. The SLiM-CRAB criteria address this issue by incorporating additional parameters, such as the presence of clonal bone marrow plasma cells ≥60%, involved/uninvolved serum free light chain ratio ≥100, or >1 focal lesion on magnetic resonance imaging or positron emission computed tomography. These criteria enable the identification of asymptomatic patients at higher risk of progression and facilitate early intervention, leading to improved outcomes.[23]

Implications of early detection and prognostication for achieving a functional cure

Another crucial aspect of achieving cure in MM is accurate prognostication. MRD has emerged as a treatment goal for NDMM and relapsed disease. Highly sensitive techniques, such as next-generation flow cytometry or next-generation sequencing, can detect residual malignant plasma cells and provide valuable information about disease burden and treatment response. MRD negativity, meaning the absence of detectable disease, has been associated with better outcomes and prolonged progression-free survival and overall survival. By utilizing MRD assessment, clinicians can tailor treatment strategies based on individual response, intensifying therapy for patients with persistent MRD positivity or de-escalating treatment for those achieving deep MRD negativity. This personalized approach may significantly improve the chances of achieving functional cure in MM.

Representative current trials implementing MRD testing in treatment decision-making are summarized in Table 3.

Furthermore, advances in sequencing technologies, such as affordable whole-genome sequencing and multi-omic single-cell assessment of malignant plasma cell as well as non-malignant cells of the surrounding microenvironment, have transformed our understanding of the molecular landscape of MM.[24-26] These techniques allow for comprehensive analysis of the genetic alterations and clonal heterogeneity present within tumor cells. Whole-genome sequencing provides a detailed view of the entire DNA sequence of a patient's tumor, enabling the identification of potential driver mutations, therapeutic targets but also modes of resistance to targeted therapies such as chimeric antigen receptor (CAR) T cells and personalized treatment approaches. Single-cell sequencing takes this analysis a step further by characterizing the genetic and phenotypic heterogeneity within individual tumor cells. These advanced genomic techniques have provided important insights into disease progression, treatment resistance and mechanisms of relapse. By deciphering the underlying genetic complexity of MM, clinicians can develop targeted therapies and personalized treatment regimens that address the unique molecular characteristics of each patient's disease in order to eradicate MRD. Single-cell and whole-genome sequencing approaches have been successfully used to study modes of resistance to anti-B-cell maturation antigen (BCMA) CAR T cells[27,28] and to predict the response to T-cell-engaging therapies (Table 4, Figure 2).[29]

Nevertheless, as yet, personalized/tumor agnostic approaches in MM have largely failed: for example, in a recent study by Andreozzi *et al.*,[30] survival intervals were comparable in the groups treated using an agnostic ("molecular-oriented") approach or according to physicians' choice. It should be mentioned that a weakness of this study was the limited number of patients treated with the molecular-oriented approach, and there were other challenges in MM such as the high mutational load, plasma cell heterogeneity and absence of unifying driver events.[31] Widespread biomolecular techniques and improvement of treatment algorithms could nevertheless improve selection for precision medicine, a vision of personalized or molecularly-driven treatment that cancer experts are striving to achieve in MM as well.[31]

In addition to enhancing early detection and prognostication, these advances have also paved the way for further development of novel therapeutic approaches in MM. Precision medicine, which focuses on tailoring treatment to an individual's unique genetic profile, has gained significant momentum with the integration of genomic technologies. The identification of specific genetic alterations and dysregulated pathways in myeloma cells has allowed the development of targeted therapies aimed at disrupting these mechanisms. For example, detection of the *BRAF* V600E mutation provides a therapeutic opportunity;[32,33] other examples include the novel peptide drug conjugate melflufen[34] and the potent cereblon E3 ligase modulator, mezigdomide.[35]

Treatment strategies for potentially achieving cure

Although the approval of every new agent for the treatment of NDMM challenges the continued role of ASCT, delineating transplant-eligible (TE) from transplant-ineligible (NTE) patients remains an important step to define first-line therapy in MM. The latest studies comparing novel agent-based triplet-drug regimens alone or in combination with ASCT and continued maintenance until progression still favor ASCT, especially with regard to a progression-free survival benefit.[36,37] Importantly, however, to date, no overall survival benefit has been shown in the large, randomized studies with mature follow-up when compared to delaying transplant and/or keeping it in reserve. However, including a CD38 monoclonal antibody during induction therapy has led to unprecedented rates of deep remissions before and after ASCT.[38-41] Results from trials investigating quadruplet induction regimens alone (Cepheus: NCT03652064) or in combination with ASCT (ISKIA: NCT04483739 and Perseus: NCT3710603) (Table 3) are now available and confirm the benefit of the latter approach.[42,43] Therefore, induction therapy with a CD38 antibody in combination with a proteasome inhibitor, immunomodulatory drug and dexamethasone followed by ASCT and lenalidomide maintenance can be considered a standard of care for most TE NDMM patients today. The high rates of sustained MRD-negativity following such an intensive treatment regimen - especially in standard-risk patients – legitimizes optimism towards a higher proportion of functional cures compared to those previous reported for TE patients before the introduction of quadruplet induction regimens. There are currently several ongoing trials recruiting NDMM patients which are investigating intensive frontline therapies and MRD testing aimed at achieving functional cure, at least in standard-risk patients (Table 3). Whether or not functional cure can also be achieved in NTE patients is also currently under consideration. Data from the MAIA and ALCYONE phase III clinical trials that incorporated daratumumab into treatment of NTE, NDMM patients demonstrated encouraging MRD negativity rates even in frail patients.[44-48] However, longer follow-up is needed to show whether subgroups of patients enrolled in novel frontline trials with CD38 antibodies can achieve long-term, sustained complete remission and hence potential functional cure.

Novel therapies and combination approaches with potential for cure

While ASCT has been a valuable option for TE patients, most patients with NDMM are deemed not eligible for various reasons. However, recent advances in immunotherapy, specifically CAR T-cell therapy and bispecific antibodies, offer promising alternatives that may revolutionize the treatment landscape for myeloma patients, including those who are unable to undergo ASCT. Several clinical trials investigating BCMA-targeted CAR T cells have demonstrated promising

outcomes.[49-55] Early-phase studies have reported deep and durable responses, even in heavily pretreated patients with relapsed or refractory myeloma. Remarkably, some patients achieved sustained MRD negativity.[51] While the long-term durability of CAR T-cell therapy in myeloma is still being evaluated, emerging evidence suggests it could provide a potential curative option, also for NTE patients. Currently, there are several clinical trials investigating the role of CAR T-cell therapy in frontline treatment for TE and NTE patients. These trials will not only answer the question of whether CAR T-cell therapy will replace ASCT, but will also provide evidence on whether CAR-T cell therapy represents a curative option in MM. Despite the significant advances of CAR T-cell therapy, there are several unanswered questions that

Table 4. Possible changes in multiple myeloma: past, present, future and implications that may allow prolonged remission and possible cure.

MM parameters		Past	Present	Future	Implications
MM diagnostics	Staging system	Durie & Salmon	ISS → R-ISS + SLiM-CRAB	Inclusion of molecular-determined risks	Allowing earlier MM treatment start
	Disease burden measurement	M-gradient, X-ray examination of the bone	M-gradient quantification, Sensitive imaging (WB-CT, MRI, PET-CT), Mass spectrometry, Circulating PC, tumor-DNA in PB + BM, MRD in PB + BM, Molecular diagnostics (WGS)	Further refined imaging Deeper MRD PB diagnostics WGS	Disease burden detected earlier → treatment advanced quicker
Treatment-related factors	Treatment start	With symptoms, i.e. CRAB	SLiM-CRAB, In studies: HR-SMM	?	Less "iceberg" to be diminished
	Therapy duration	For 4-6 cycles	Until progression	Defined treatment stops	With longer treatment → deeper + prolonged remission induction Stop treatment in cured patients
	Therapy options	Limited	Many options, combination partners, numerous clinical trials, IO: moAb, ADC, BITE, CAR T cells, quadruplet regimens and "5-agent combinations"	Cure combinations?	Almost limitless treatment options
	Therapeutic goal	Symptom control, MM- stabilization or decrease	In young + fit: CR + as deep and prolonged remission as possible In elderly and unfit: disease control	Cure options in both young and elderly	-
	Therapy lines	Less often: beyond 3	6-10 not uncommon	Cure or chronic disease transformation	-
	Relapse → start of retreatment	With CRAB=MM symptom recurrence	With serological progression	With MRD reversal from negative → positive?	Less disease burden needing to be diminished
Patient-related factors	Pts constitution	Fit pts: being treated Unfit: BSC	Fit and unfit pts defined with treatment options for both	Unfit pts made fit again?	-
	Transplant limits	<60-65 years	≥70 years, if tested fit	Transplants deceasing?	-
Outreach approaches	Center-related	Center-focused MM treatment	International exchanges, comprehensive cancer centers, IMWG/EMN consortia	Entire worldwide exchange	-
Prognosis	Changes in PFS + OS	3-5 years	8-10 years	>10 years → cure	Much better prognosis

MM: multiple myeloma; ISS: International Staging System; R-ISS: Revised International Staging System; SLiM-CRAB: ≥60% bone marrow plasma cell infiltration, serum free light chain ratio ≥100, >1 magnetic resonance imaging-defined focal lesion, hypercalcemia, renal impairment, anemia, bone lesions; WB-CT: whole body computed tomography; MRI: magnetic resonance imaging; PET-CT: positron emission tomography-computed tomography; PC: plasma cells; PB: peripheral blood; BM: bone marrow; MRD: measurable residual disease; WGS: whole genome sequencing; HR-SMM: high-risk smoldering multiple myeloma; IO: immune oncology therapies; moAb: monoclonal antibodies; ADC: antibody drug conjugates; BITE: bispecific antibodies; CAR: chimeric antigen receptor; pts: patients; EMN/IMWG: European Myeloma Network/International Myeloma Working Group; PFS: progression-free survival, OS: overall survival.

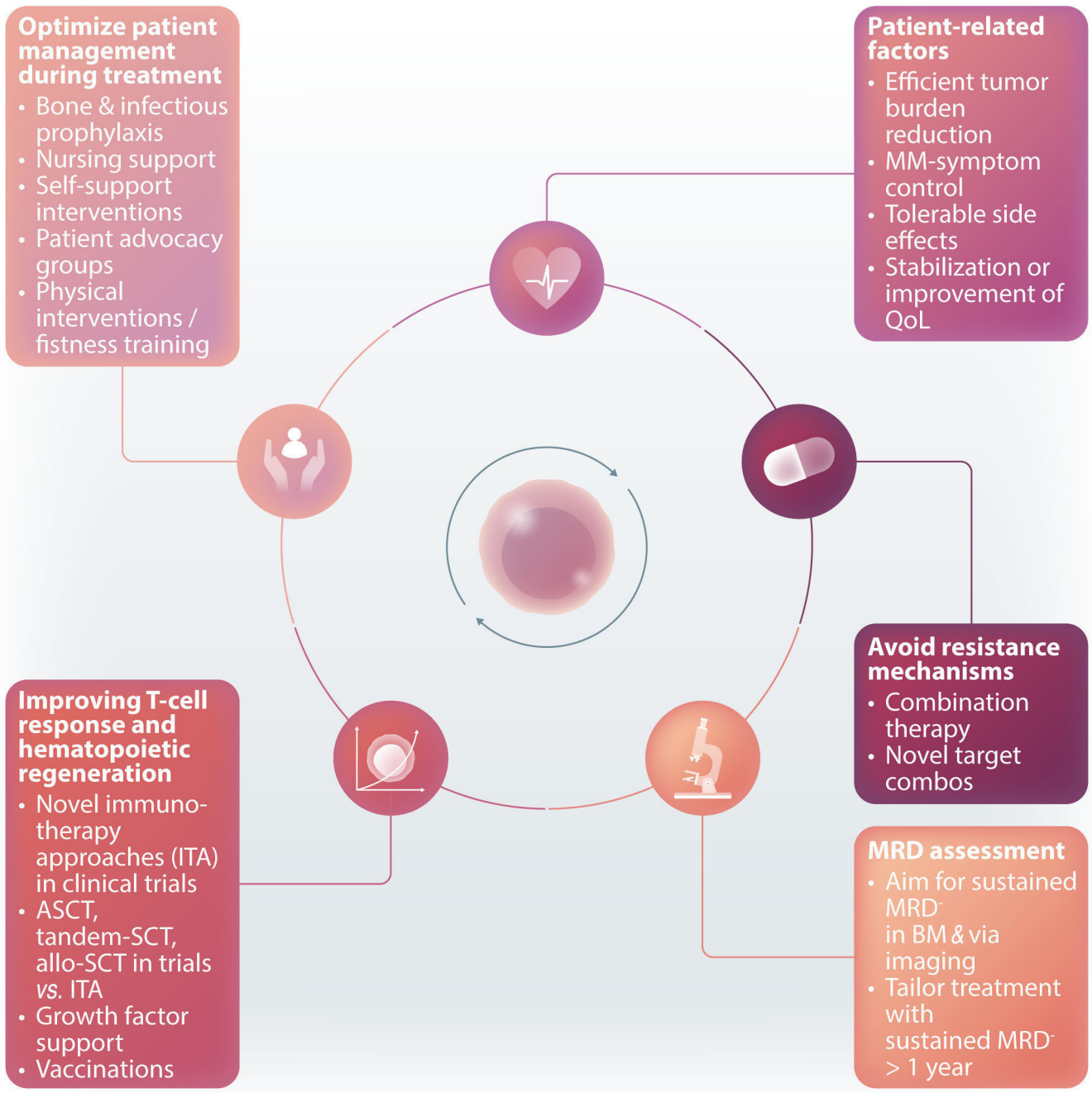

Figure 2. Strategies to attain a cure or operational cure in multiple myeloma. MM: multiple myeloma; QoL: quality of life; combos: combinations; MRD: measurable residual disease; BM: bone marrow; y: year; ASCT: autologous stem cell transplantation; allo-SCT: allogeneic stem cell transplantation.

need to be addressed in the future. Besides clinical factors that need to be defined to identify patients who might profit most from CAR T-cell therapy, there are also socioeconomic challenges that require thorough assessment. These are related to the limited availability of manufacturing slots, the substantial costs and financial burdens for individuals and healthcare systems as well as regional and racial disparities when it comes to access to CAR T-cell therapy or other higher-priced therapy options.[56-59] Even if CAR T-cell treatments do provide a potentially curative option for MM patients, only a relatively small number of privileged patients in certain regions of the world with well-resourced healthcare jurisdictions can currently derive benefit from this important innovation.[56,58,59]

Bispecific antibodies represent another novel therapeutic approach that holds significant potential in MM treatment. Major advantages of this approach, compared to CAR T-cell-based therapies, include the immediate "off-the-shelf" availability and the broader availability outside tertiary centers, although these treatments remain costly and still require additional hospitalization for step-up dosing. These engineered molecules simultaneously bind to tumor-associated antigens, such as BCMA, GPRC5D and FcRH5 on MM cells and CD3 on T cells, facilitating the formation of a cytotoxic immune synapse.[60] By bridging cancer cells and immune cells, bispecific antibodies enhance the immune system's ability to target and eliminate malignant plasma cells. Early clinical trials with bispecific antibodies, showing unprecedented rates of long-lasting and deep remissions in relapsed or refractory MM patients previously treated with triplet regimens, have led to the approval of teclistamab and talquetamab by the Food and Drug Administration as well as the European Medicines Agency and other bispecific antibodies are expected soon.[61,62] Ongoing trials are now investigating bispecific antibodies in combination with established anti-myeloma drugs in earlier lines of treat-

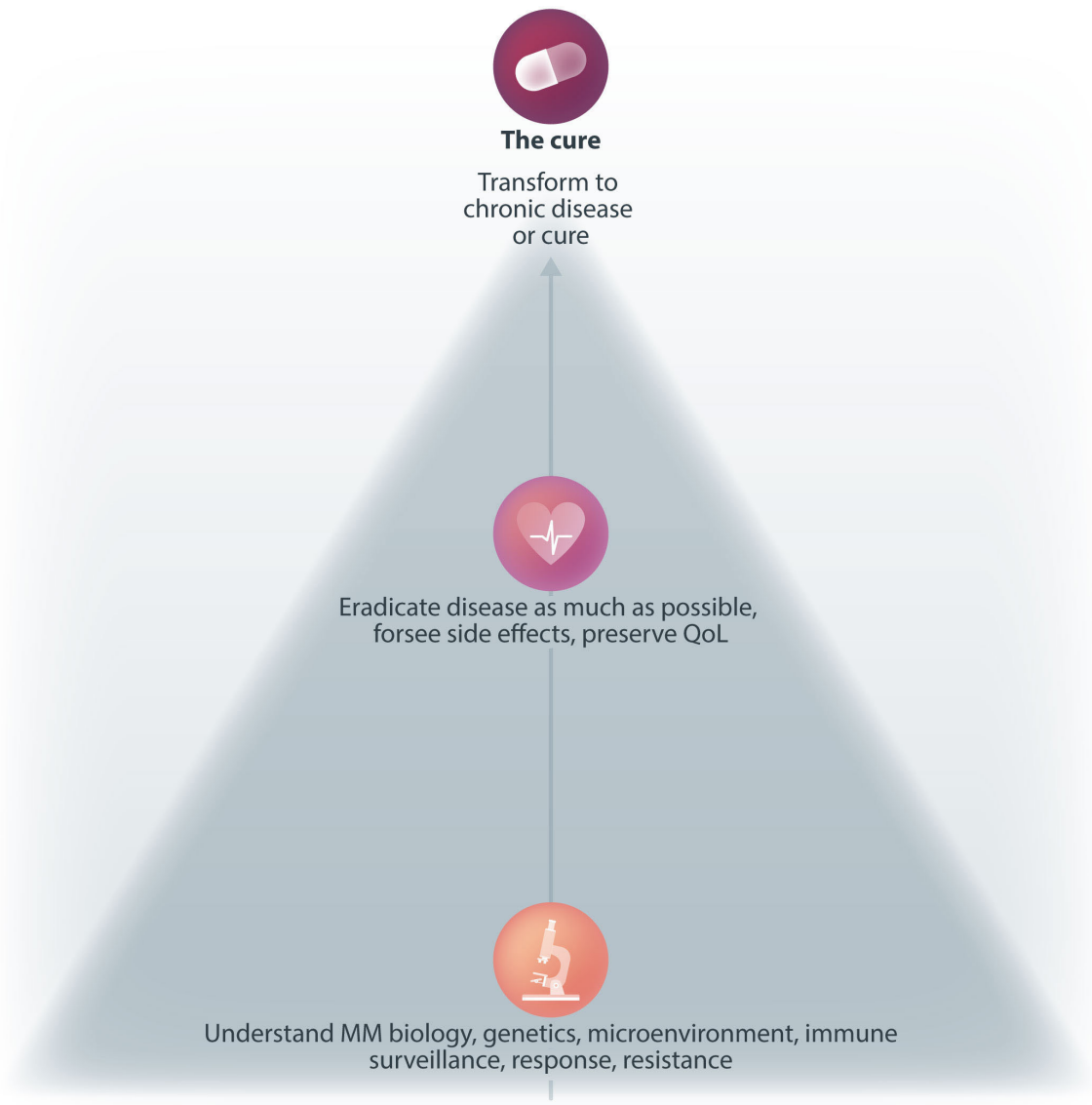

Figure 3. Future strategies to achieve cure in 1-10% of multiple myeloma patients. MM: multiple myeloma; QoL: quality of life.

ment. Preliminary results from these clinical trials and the unprecedented rates of MRD negative remission in heavily pretreated relapsed or refractory MM patients support optimism regarding effectiveness in earlier disease. Unanswered issues regarding the use of bispecific antibodies include the optimal treatment duration and intensity and the prevention of severe side effects, especially the high rate of life-threatening infections.[63] These points need to be addressed to definitively include bispecific antibodies in curative treatment strategies, since a patient who is still under continuous treatment and susceptible to potentially fatal side effects such as overwhelming infection cannot reasonably be considered cured. New strategies, including fixed duration of treatment, accompanied by a thorough program to mitigate infectious complications as one example, are clearly warranted.

Patient factors and barriers to cure

Age, fitness, and other factors that impact treatment

While advancements in diagnostic, prognostic and treatment options have improved outcomes for many patients, individual characteristics can have an impact on the effectiveness of therapies and the overall chances of achieving cure. Advanced age is often associated with poorer outcomes in MM.[64] Older patients may have comorbidities and reduced physiological reserves, making them more susceptible to treatment-related toxicities and complications.[10,64] However, it is important to note that chronological age alone should not dictate treatment decisions, as shown in numerous prospective and retrospective analyses of both ASCT and non-ASCT patients. In a study by Straka *et al.*,[65] patients up to the age of 70 years were randomized to no induction but upfront melphalan 140 mg/m^2 and tandem ASCT or standard induction and tandem ASCT. Various aspects of the study were noteworthy, such as the number of patients (n=434) included, their more advanced age for tandem ASCT (60-70 years), the double transplant approach, and short treatment duration (7.7 months with induction and 4.6 months without induction). On an intention-to-treat basis, median progression-free survival times in patients given or not given induction were comparable, being 21.4 and 20.0 months, respectively (P=0.36). Patients aged ≥65 years (55%) did not have an inferior outcome. Patients with low-risk cytogenetics, i.e., those without del17p13, t(4;14) or 1q21 gains, had a favorable overall survival. In another study from Germany presented by Straka at the annual meeting of the American Society of Hematology

in 2022, 348 patients between the age of 60-75 years were randomly assigned to either continuous treatment with lenalidomide/dexamethasone or the same drugs given in three cycles of induction therapy followed by reduced-intensity (melphalan 140 mg/m^2) single or tandem ASCT and lenalidomide maintenance.[66] While there were no significant differences in progression-free and overall survival between the two groups after a median follow-up of 68 months, encouraging median overall survival times of 87 and 96 months, respectively, were observed, highlighting that even before the introduction of anti-CD38 antibodies, elderly patients had a meaningful likelihood of experiencing long-term remission. These data also demonstrate that in certain subgroups of patients, the clinical benefit from the addition of intensive chemotherapy and ASCT may be limited. A similar observation was made in the DETERMINATION study, in which African-American patients failed to achieve the same gain in progression-free survival as others, and appeared to do better with ASCT being kept in reserve.[67] Therefore, the overall health status, other pathobiological conditions, and functional age of patients should always be considered.[67] Several scoring systems to quantify fitness and frailty in MM have been established in order to objectify biological health.[10,64,68,69] While frail patients are usually not considered eligible for transplants, the introduction of CD38 monoclonal antibodies led to improved outcomes in this difficult-to-treat population[70,71] which usually represents the largest portion of patients treated outside of clinical trials and tertiary centers, given that the median age at diagnosis of MM is approximately 70 years.[72] Future studies will show whether functional cure can only be achieved in fit patients or whether adaptive and/or adoptive immunotherapy such as CAR T cells and bispecific antibodies may provide similar functionally curative options for elderly and/or frailer patients.[73]

Psychological and social support can also significantly impact a patient's ability to cope with the challenges of MM treatment.[74] Patients with robust support networks, exercise and fitness training,[69,75,76] and access to psychological support services often adhere to treatment better, have better quality of life and potentially better treatment outcomes.[77] Additionally, patients who are embedded in a stronger social support system might more readily gain access to novel therapies, including clinical trials, not least through the encouragement, advocacy and support of a caring family and friends.

The role of supportive care in achieving cure

With the increasing number of available agents to treat MM and the higher rates of deep, long-lasting remissions, supportive care remains vitally important in the management of MM, especially with the aim of long-term control and/or functional cure of the disease. Historically, symptom management such as alleviating bone pain, addressing side effects including peripheral neuropathy and improving bone health with bisphosphonates or receptor activator of nuclear factor -κB ligand (RANKL) antibodies have been at the center of supportive care in MM.[78] To ensure that patients re-enter their normal life after the diagnosis and potentially curative treatment, additional areas need to be addressed. Supportive measures should include psychological counseling, exercise programs, psychotherapy, support groups, and relaxation techniques to address physical fitness, emotional distress, anxiety, depression and fears associated with the disease. Additionally, the importance of diet on general health and its effect on deep remission and follow-up treatment have been recognized in recent years.[79] Beneficial effects of plant-based diets have been shown in NDMM[80] and fasting diets may be associated with improved immune function in cancer patients, making this an important and exciting area of study in MM.[81] Maintaining adequate nutrition is crucial for optimizing treatment outcomes and supporting the body's ability to tolerate therapy. Nutritional counseling and support from dietitians can help address dietary deficiencies, manage treatment-related changes in taste or appetite, and provide guidance on maintaining a healthy diet during and after treatment.

Preventing infections and managing them optimally is another highly crucial aspect of supportive care in the journey of any MM patient and particularly that towards the goal of potential functional cure for MM.[63] Patients with MM are particularly susceptible to infections due to immune system dysfunction caused by the disease itself and treatment-related immunosuppression. Prophylactic measures, such as antimicrobial and antiviral agents as well as vaccinations following treatments, are mandatory (such as in the first 6 months following ASCT or CAR T-cell therapy to reduce the risk of infections and their associated complications).[63] Additionally, intravenous immunoglobulin substitution therapy should be considered in most cases,[82] especially in patients treated with CAR T-cell therapy and bispecific antibodies. Intravenous immunoglobulins, derived from pooled human plasma, contain antibodies that provide passive immunity against various infectious agents. For myeloma patients with hypogammaglobulinemia (e.g. IgG <400 mg/dL) or recurrent severe infections, intravenous immunoglobulins should be administered monthly and typically over at least 6 months to supplement deficient antibodies and reduce the risk of infections.

Ideally, these safety measures should be implemented during the first months following a potentially curative treatment and then discontinued after recovery of the patient's immune system. However, long-term data on immune reconstitution following CAR T-cell therapy and discontinuation of bispecific antibodies after achieving a deep and sustained remission are currently being collected and are required before definitive recommendations can be made.

Advances in genomics and personalized medicine

Deciphering the human genome cost approximately one million US dollars in 2007. The cost has now decreased to several hundred US dollars per patient. Furthermore, novel single-cell multi-omic analyses have been developed to study tens of thousands of malignant myeloma cells and non-malignant individual cells to better characterize an individual's immune system. These developments are leading to a better understanding of outcome with novel immunotherapies to reveal modes of resistance to treatment. Examples are the pretherapeutic T-cell landscape, which is related to response to bispecific antibodies,[29] and the biallelic loss of antigens such as BCMA on MM cells.[27,28] Additionally, the respective genetic information may be used in the future for personalized treatment decisions based upon these findings. Examples include targeting the *BRAF* V600E mutation as well as the effectiveness of BCL2 inhibitors in patients with high BCL2 expression in malignant plasma cells, as often but not exclusively observed in patients harboring a (11;14) chromosomal abnormality.[83] However, malignant plasma cells are not homogeneously distributed within the patient. Therefore, the emerging concept of spatial genomic heterogeneity needs to be addressed,[84-87] especially when aiming to eradicate MRD and potentially cure patients with MM.[88] As personalized approaches continue to evolve, the ability to translate clinical trial findings into real-world practice is likely to improve.[89]

Implications of curing multiple myeloma for healthcare systems and society as a whole

Introducing the goal of cure into myeloma care has obvious implications for our healthcare systems and for society in addition to profound consequences for each MM patient. The incidence and prevalence of MM has increased significantly over the last several decades.[90] Given the improved diagnostic and therapeutic options now available, there are changes in strategy from the past to the future aiming for functional cure, as summarized in Table 4.

Patients are now diagnosed earlier and survive longer with their disease than in the past.[23] However, current treatments are applied until progression, which supposes a significant burden on healthcare resource utilization. The vision of curing MM patients and ultimately achieving a fixed duration of treatment would not only alleviate side effects but would also be more cost effective compared to continuing the application with multiple lines of therapy. In addition to this cost reduction, curing myeloma would also have implications for healthcare resource allocation. Currently, MM requires long-term treatment and management which places a substantial burden on healthcare providers. Achieving a functional cure of MM would enable these resources to be redirected to other areas of need so easing the demands on hospital resources and reducing the needs for ongoing treatment. Furthermore, when an individual develops MM this can lead to reduced productivity and possible unemployment due to treatment-related side effects and physical limitations.[4,69,91] Ultimately fostering a cure for MM would empower patients and the community, and instill positivity, so inspiring others with, not least, reinforcement of belief in the value of medical science, and its potential for overcoming great and seemingly impossible challenges.

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Contributions

ME and MM wrote the paper and performed the analysis as displayed in the Tables and Figures. MM, HG, MKK, and ME designed the analysis and revised the data. All authors approved and carefully corrected the paper.

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Data-sharing statement

The data that support the findings of this review are available from the corresponding authors (ME, MM) upon reasonable request.

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