High-risk multiple myeloma: how to treat at diagnosis and relapse?

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Patients with multiple myeloma have experienced a great improvement in survival over the past century because of the introduction of novel therapeutic strategies. However, a subgroup of patients with poorer outcomes than expected is considered high risk and identified by the presence of patient- and disease-based factors such as frailty, extramedullary disease, cytogenetic abnormalities, or even relapses occurring earlier than expected according to the baseline factors. Although the management of patients with high-risk features is not well established because of the lack of specific trials in this subgroup of patients and because of their underrepresentation in the clinical trials, treatment should be planned on 2 pillars: (1) poor prognosis with the presence of high-risk features can be at least improved or even abrogated by achieving a deep and sustained response over time, and (2) this can most likely be obtained through using the best therapeutic options and in a response-adapted way. Some clinical trials that have been planned or are ongoing include only patients with high-risk features, using the most effective therapies (proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies) as well as chimeric antigen receptor T cells and T-cell engagers that will unravel what the best therapeutic approach will be to overcome the poor prognosis of the presence of high-risk features.

LEARNING OBJECTIVES

- Identify high-risk myeloma based on patient-, disease-, or outcome-based factors
- Be able to define the key objectives to overcome poor prognosis with the presence of high-risk features
- Define the best therapeutic strategy for patients with high-risk features

CLINICAL CASE

A 48-year-old man with newly diagnosed (ND), Revised International Staging System (R-ISS) III (ISS III plus del(17p)), Bence-Jones κ multiple myeloma (MM) sought treatment and consultation for MM that had been diagnosed in another institution. The patient had an active lifestyle, and the workup showed mild anemia and small lytic lesions in the pelvis and femora as myeloma-defining events. His Eastern Cooperative Oncology Group performance status was 1. He was treated with 6 induction cycles of lenalidomide, bortezomib, and dexamethasone (RVd), achieving a very good partial response, followed by high-dose melphalan and autologous stem cell transplantation (HDM-ASCT), achieving stringent complete remission (sCR) with minimal residual disease (MRD) positivity. He rejected a second ASCT and proceeded to consolidation with 2 cycles of lenalidomide, carfilzomib, and dexamethasone, achieving sCR and MRD negativity. Maintenance with lenalidomide was prescribed. Twelve months after starting maintenance therapy, relapse occurred with reappearance of the M-component in urine. He was included in a clinical trial and treated with B-cell maturation antigen (BCMA) chimeric antigen receptor T (CAR-T) cells, and a new sCR and MRD negativity were achieved. The patient continues in follow-up.

How do we define high-risk patients with MM?

Table 1 summarizes the most relevant patient- and disease-based factors to define high-risk patients.

Patient-based factors

Frailty

For a long time, chronological age influenced treatment decisions, and the outcome was poor for the elderly. The International Myeloma Working Group (IMWG), through a pooled analysis including 869 ND elderly patients enrolled in clinical trials, built a simplified geriatric score

Table 1. Patient- and disease-based factors for the identification of high-risk MM

High-risk features	Definition
Patient-based factors	
Frailty status	IMWG frailty score Modified IMWG frailty score R-MCI GAH
Disease-based factors	
Aggressiveness in the clinical presentation	Extramedullary disease (no bone-related plasmacytomas) Plasma cell leukemia LDH elevated
Cytogenetic abnormalities	del(17p), t(4;14), t(14;16), amp1q, del(1p)
Mutations	*TP53*
Biochemical abnormalities	LDH elevated β2-microglobulin ≥5.5mg/L Albumin levels ≤3.5mg/L
Prognostic scores	
R-ISS	R-ISS III: beta2-microglobulin ≥5.5mg/L plus either LDH elevated or high-risk CA (del(17p), t(4;14), or t(14;16))

GAH, geriatric assessment in hematology; R-MCI, Revised Myeloma Comorbidity Index.

based on age, comorbidities, and cognitive and physical conditions to distinguish among fit (score = 0), intermediate fitness (score = 1), and frailty (score ≥ 2). Frail patients showed a significantly shorter overall survival (OS; 57% at 3 years) than unfit (76% at 3 years) and fit patients (84% at 3 years).[1] Many clinical trials are using an IMWG-modified frailty model to identify frail patients because of the importance of their identification for the treatment decision-making process.[2]

Disease-based factors

Features associated with disease aggressiveness

The presence of extramedullary disease (EMD) or plasma cell leukemia (PCL), primary or secondary, is infrequent, but these are considered high-risk features not only because the plasma cells escape from the bone marrow environment but also because patients with EMD or PCL are difficult to treat, with poor outcomes with the current therapies (3-year survival rate is 35% for EMD[3] and median OS is 12 months for PCL[4]).

Cytogenetic abnormalities

The IMWG currently recommends the detection of t(4;14), t(14;16) and del (17/17p) in selected plasma cells by interphase fluorescent in situ hybridization for the identification of high-risk patients.[5] In newly diagnosed MM (NDMM), the presence of at least 1 high-risk cytogenetic abnormality (CA) is associated with a median OS of 24.5 months, significantly shorter than the 50.5 months observed when there are not any CAs ($P < .001$). This is far from complete and requires being updated.

The gain of the long arm of chromosome 1 (+1q) is a frequent CA observed in approximately 30% of NDMMs and associated with poor outcome. A retrospective study conducted in 201 patients with NDMM treated with RVd reported that patients harboring +1q had a shorter median progression-free survival (PFS; 41.9 months) and OS (not reached) compared with those without +1q (PFS of 65.1 months, $P = .002$ and OS not reached, $P = .003$). The negative impact on survival with +1q may be more profound if there is amplification of 1q, defined by the presence of 4 or more copies of chromosome 1q (median PFS of 25.1 months) or in association with other high-risk CAs (median PFS of 34.6 months). The poor prognosis of patients who have +1q with a coexisting deletion of chromosome 1p (del(1p)) has also been described.[6]

Although it is well accepted that del(17p) is the CA with more prognostic impact in MM, some questions are under debate: (1) What is the optimal threshold to predict poor prognosis? (2) Is *TP53* an optimal molecular target? (3) What about mono- or biallelic deletion and/or inactivation of *TP53* through mutations? Patients with a "double-hit" biallelic inactivation of *TP53* are at high risk, especially if this abnormality coexists with ISS 3 (1.5-year PFS of 33%) in ND patients.[7] The Intergroupe Francophone du Myélome (IFM) has recently reported in a large series of patients with NDMM that the presence of isolated del(17p) was also associated with a poor outcome, although the poorest outcome was reported for the double-hit patients.[8]

In summary, the optimal identification of high-risk MM based on CA is under construction, but in clinical practice, the CA recommended by the IMWG, together with abnormalities of chromosome 1 and mutational status of *TP53,* if possible, would be necessary to define the risk at baseline. At the moment of the relapse, it would be optimal to repeat these evaluations because of the clonal evolution and the potential acquisition of new CAs not detectable at baseline.

R-ISS

The ISS risk model, including albumin and β2-microglobulin levels, was improved with the incorporation of 2 well-known disease-related prognostic biomarkers, CA and serum lactate dehydrogenase (LDH) levels, which are associated with a higher proliferative activity, resulting in the R-ISS model.

The R-ISS emerged from a large series of patients with NDMM, and 3 subgroups were defined: R-ISS I (n = 871), including ISS stage I, no high-risk CA, and normal LDH level with a 5-year OS rate of 82%; R-ISS III (n = 295), including ISS stage III and high-risk CA or high LDH level with a 5-year OS of 40%; and R-ISS II (n = 1894), including all the other possible combinations and with a 5-year OS of 62%.[9] This staging system is still valid, although there are some limitations: (1) most patients were assigned to the R-ISS II, including those with high-risk CA but not ISS III, (2) some other high-risk CAs such as +1q were not included, and (3) other, more complex genomic abnormalities such as mutations or inactivation of *TP53* were not considered.

Functional high-risk patients

In addition to the above high-risk features, how do we recognize those patients with no apparent high risk at diagnosis but who progress within the first 12 to 18 months after an optimal first line of therapy? These patients are functional high risk with poor prognosis, and further investigations are required to unravel if there is a clonal selection or just an inadequate evaluation at diagnosis.

What is the optimal management for patients with high-risk features?

If the identification of high-risk patients with MM is challenging, its management is not easy either. So far, only a few clinical

trials have been specifically conducted in this population because the definition is heterogeneous. In addition, high-risk subgroups in clinical trials are quite small to generate solid recommendations.

In 2021, we know that poor prognosis with the presence of high-risk features can be at least improved or even abrogated by the achieving a deep and sustained response over time, which can most likely be obtained through the use of novel therapeutic options.[10]

At least 3 large meta-analyses support the use of MRD for monitoring the response in MM because of its prognostic value. The most recent one included publications up to June 2019, showing that the achievement of undetectable MRD improved PFS (hazard ratio [HR], 0.33) and OS (HR, 0.45) in comparison with the presence of MRD. Moreover, its prognostic impact was sustained across the different subgroups, including those with some high-risk features such as elderly patients with NDMM, relapsed/refractory patients, or even the presence of high-risk CA.[11]

Of note, the higher the sensitivity threshold for the MRD evaluation and the longer the sustained undetectable MRD over time, the higher the prognostic value.

In addition, the achievement of undetectable MRD can convert risk assessment in MM into something dynamic, and the high risk at baseline can be overcome when undetectable MRD is achieved. In the PETHEMA/GEM2012MENOS65 trial, 458 patients with NDMM had longitudinal assessment of MRD after 6 induction cycles with RVd, autologous transplantation, and 2 consolidation courses with RVd. The 3-year PFS rate for patients with R-ISS I, II, or III was comparable (95%, 94%, and 88%) if MRD was undetectable after treatment. By contrast, outcomes were progressively poor for patients with R-ISS I, II, and III when MRD was detectable, with a 3-year PFS of 62%, 53%, and 28%, respectively, and analogous results were observed when OS was considered. Similarly, outcome of patients with high-risk CA was abrogated when undetectable MRD was achieved.[12]

One additional aspect needs to be incorporated in the MRD assessment: the MRD evaluation outside of the bone marrow through the use of functional imaging tools such as positron emission tomography/computerized tomography.[13] Deauville scores to focal lesions less than 4 and bone marrow uptake showing the liver background (Deauville score <4) have been identified as the best cutoff to define positron emission tomography/computerized tomography negativity after therapy and complete metabolic response, as they have been described in at least 2 clinical trials, the FORTE and CASSIOPETT substudy of CASSIOPEIA trial.

Management of frail patients

The general approach described above is feasible for frail patients, but tolerability and quality of life are crucial to deliver treatments in order to reach depth responses. At least 1 clinical trial has been conducted in unfit and frail patients with NDMM according to the IMWG frailty index, using ixazomib and daratumumab plus very low dose of dexamethasone.[14] Preliminary results are encouraging, with 1-year OS rates of 96% and 74% for unfit and frail patients, respectively. Subgroup analysis recently conducted in the phase 3 trials ALCYONE and MAIA have also shown how the addition of daratumumab to either bortezomib, melphalan, and prednisone (VMP) or Rd (lenalidomida and dexamethasone) has been able to significantly improve the outcome of frail patients compared with VMP or Rd alone, according to a modified IMWG frailty index (Table 2). In the relapsed-refractory setting, other subanalyses of phase 3 clinical trials have reported how carfilzomib at different doses and schedules or the combination of pomalidomide-dexamethasone plus isatuximab is feasible and able to improve the outcome of frail patients.[15,16] Although this information is obtained from clinical trials, the good toxicity profile of all novel agents makes it possible to maintain therapy in the frail population.

Management of patients with high-risk CA or R-ISS III with approved drugs

Proteasome inhibitors (PIs), immunomodulatory drugs, and corticosteroids are the key treatment elements of patients with MM patients with high-risk CA. For transplant-eligible patients with NDMM, the question about bortezomib or carfilzomib as the optimal PI for high-risk patients remains under debate because the only phase 3 randomized trial comparing bortezomib with carfilzomib did not show any difference, but it did only include patients with t(4;14).[17]

The use of moAbs (monoclonal antibodies) targeting SLAMF7 and CD38 also has been evaluated in this setting. Although the addition of elotuzumab showed no significant benefit when combined with RVd in the phase 2 SWOG-1211 study,[18] the addition of daratumumab has been shown to improve the outcome of patients with NDMM and RRMM (relapsed refractory multiple myeloma) with high-risk CA in a recent meta-analysis.[19] HDM-ASCT continues to be the standard of care in high-risk NDMM because of its capacity to achieve a higher undetectable MRD rate, and tandem transplant is even considered for this population based on the positive data from the EMN02 trial, confirmed in the STAMINA trial at least in terms of PFS.[20,21] However, tandem transplant may not be necessary with the introduction of moABs, especially with the introduction of cell therapy. Maintenance with lenalidomide is the standard of care to improve the outcome of high-risk patients compared with observation, but it should be improved through the addition of PIs or moABs, with preliminary positive data.[22,23]

In the nontransplant-eligible, high-risk patients with NDMM, daratumumab, lenalidomide, and dexamethasone would be the first choice based on the results reported in the MAIA trial, with a median PFS of 45.3 months compared with 29.6 months in the Rd arm (HR, 0.57).[24]

In the RR (relapse or refractory) setting, the same approach is valid, and the combination of choice for patients with high-risk CA would be those with the higher likely probability of achieving undetectable MRD (Table 2).

Of note, the novel drug melflufen flufenamide has shown promising efficacy in 45 patients with EMD (extramedullary disease) included in the HORIZON trial, with an overall response of 24% vs 30% in patients without EMD.[25] Selinexor also may have a role in treating patients with del(17p) based on its mechanism of action and available evidence in some clinical trials.[26] Belantamb mafodotin, a BCMA-conjugated moAb, produced a response rate of 33%, which is similar to that reported in patients with high-risk cytogenetics.[27] Further studies are required to confirm this efficacy. Table 2 shows the efficacy reported in patients with high-risk CA in the most relevant clinical trials in patients with NDMM and RRMM.

Table 2. Clinical studies ongoing in patients with high-risk features

Registration number	Study design	Population
ND high-risk MM		
NCT03104842	Isatuximab-KRd as induction, consolidation, and maintenance	Transplant eligible or ineligible del(17p) in ≥10% of purified cells and/or t(4;14) and/or >3 copies +1q21 ISS II or III
NCT03756896	Carfilzomib, pomalidomide, and dexamethasone as maintenance after HDM-ASCT	Transplant eligible achieving at least partial response Presence of del(17p), t(4;14), t(14;16), t(14;20) PCL at diagnosis
NCT04025450	Chidamide (HDAC inhibitor)–lenalidomide, bortezomib, and dexamethasone as induction	Transplant eligible and ineligible Presence of del(17p), t(4;14), t(14;16), t(14;20) R-ISS III IgD/IgE Extramedullary plasmacytomas Peripheral plasma cells by flow cytometry ≥0.165%
NCT02128230	Induction with melphalan 20–KTD-PACE followed by melphalan 80–KTd-PACE plus ASCT and KTD-PACE consolidation and KRd maintenance (1 year) and Kd (1 year)	Transplant eligible GEP70 risk score of ≥0.66
NCT03549442	BCMA CAR-T + huCART19 in different schedules	ISS III or R-ISS III or Metaphase karyotype with >3 abnormalities except hyperdiploidy Failure to achieve partial response or better to initial therapy based on PI and IMiD
NCT04196491	BCMA CAR-T bb2121 (ide-cel) ($150–800 \times 10^6$) followed by lenalidomide as maintenance	R-ISS III
NCT04436029	Autologous $CD8^+$ T cells expressing an anti-BCMA chimeric antigen receptor	High-risk patients who completed pretransplant induction antimyeloma treatment
NCT04133636	BCMA CAR-T JNJ-68284528 (cilta-cel) followed by lenalidomide maintenance	Less than complete response after first-line treatment and transplant followed or not by consolidation
NCT04133636	BCMA CAR-T JNJ-68284528 (cilta-cel) followed by lenalidomide and daratumumab maintenance	Noneligible for transplant patients with ISS III
Relapsed-refractory high-risk MM		
NCT03601078	BCMA CAR-T bb2121 ($150–450 \times 10^6$)	R-ISS III and PD <18 months after the first-line treatment including induction, transplant, and lenalidomide maintenance PD <18 months since date of start initial therapy, which must contain PI, IMiD, and dexamethasone Less thanVGPR after induction, including PI, IMiD, and dexamethasone and transplant (between 70 and 110 days after transplant)
NCT04133636	BCMA CAR-T JNJ-68284528 (cilta-cel)	One prior line including PI, IMiD, and PD within the first 12 months after transplant or the first-line treatment for nontransplant eligible
NCT03104270	Elotuzumab in combination with pomalidomide, carfilzomib, and dexamethasone	More than 2 prior lines, including PI and IMiD and del(17p), t(14;16), t(14:20) PCL Extramedullary disease Doubling in levels of MM markers in the past 3 months Refractoriness to their most recent lenalidomide-containing regimen and PI-based regimen Renal failure with CrCl between 15 and 30 mL × minute

cilta-cel, ciltacabtagene autoleucel; CrCL, creatinine clearance; GEP70, gene expression profiling-70; HDAC, histone deacetylase; ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory drug; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide and dexamethasone; KTD-PACE, carfilzomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide; PD, progression disease; VGPR, very good partial response.

Management of functional high-risk patients

Although no specific trials were performed until very recently, new trials with BCMA-targeted CAR-T cells have focused on this subgroup of patients (Table 3). Some subgroup analysis in phase 3 trials focused on early relapses, defined as those occurring within the first 12 to 18 months after the previous therapy, showing that the addition of carfilzomib to Rd or daratumumab to Rd vs Rd in the ASPIRE and POLLUX trials resulted in a significant benefit for the triple combination compared with Rd. A similar effect has been recently reported with the addition of daratumumab to bortezomib or carfilzomib[28–31] (Table 2).

Table 3. Efficacy of current treatment approaches for patients with NDMM with high-risk features (defined as del(17p), t(4;14), or t(14;16))

	Transplant-eligible NDMM							
Clinical trial	**SWOG-1211**	**Cassiopeia**		**Forte**		**Griffin**	
Population	High risk*	ITT	High risk	ITT	High risk	ITT	High risk
Treatment	EloVRd vs VRd	DVTd vs VTD	DVTd vs VTD	KRd-T/KRd12	KRd-T/KRd12	DRVd vs RVd	DRVd vs RVd
PFS (m)/HR	**31 vs 34/0.96**	**NR/0.47**	**NR/0.67**	**NR/0.64**	**NR/0.51**	**NR/NA**	**NR/NA**

	Transplant-ineligible NDMM							
Clinical trial	**SWOG**		**ALCYONE**			**MAIA**		
Population	ITT	High risk	ITT	High risk	Frail patients	ITT	High risk	Frail patients
Treatment	VRd->Rd vs Rd	VRd->Rd vs Rd	DVMP vs VMP	DVMP vs VMP	DVMP vs VMP	DRd vs Rd	DRd vs Rd	DRd vs Rd
PFS (m)/HR	**43 vs 30/0.74**	**38 vs 16/NA**	**36 vs 18/0.50**	**18 vs 18/0.78**	**33 vs 19/0.51**	**NR vs 34/0.54**	**45 vs 29/0.57**	**NR vs 30/0.62**

	Relapsed-refractory MM									
Clinical trial	**POLLUX**			**ASPIRE**			**ELOQUENT-2**		**TOURMALINE-MM1**	
Population	ITT	High risk	Early relapse	ITT	High risk	Early relapse	ITT	High risk	ITT	High risk
Treatment	DRd vs Rd	DRd vs Rd		KRd vs Rd	KRd vs Rd		EloRd vs Rd	EloRd vs Rd	IRd vs Rd	IRd vs Rd
PFS (m)/HR	**44.5 vs 17.5/0.44**	**26.8 vs 8.3/0.37**	**0.38**	**26.3 vs 17.3/0.69**	**23 vs 13.9/0.7**	**21.4 vs 10.7/0.7**	**19.4 vs 14.9/0.70**	**NA/0.72(del17p) NA/0.56 (t(4;14)**	**20.6 vs 14.7/0.74**	**21.4 vs 9.7/0.54**

Clinical trial	**CASTOR**		**ENDEAVOR**		**CANDOR**			**IKEMA**	
Population	ITT	High risk	ITT	High risk	ITT	High risk	Early relapse	ITT	High risk
Treatment	DVd vs Vd	DVd vs Vd	Kd vs Vd	Kd vs Vd	DKd vs Kd	DKd vs Kd		IsaKd vs Kd	IsaKd vs Kd
PFS (m)/HR	**16.7 vs 7.1/0.31**	**12.6 vs 6.2/0.41**	**18.7 vs 9.4/0.53**	**8.8 vs 6.0/0.7**	**28.6 vs 15.9/0.59**	**15.6 vs 5.6/0.49**	**CRrate 28 vs 3%**	**NR vs 19.1/0.53**	**NA/0.72**

Clinical trial	**OPTIMISMM**		**BOSTON**		**ICARIA**		**ELOQUENT-3**	
Population	ITT	High risk	ITT	High risk	ITT	High risk	ITT	High risk
Treatment	PVd vs Vd	PVd vs Vd	SVd vs Vd	SVd vs Vd	IsaPd vs Pd	IsaPd vs Pd	EloPd vs Pd	EloPd vs Pd
PFS (m)/HR	**11.2 vs 7.1/0.61**	**NA/0.56**	**11.2 vs 5.8/0.61**	**NA/0.67**	**11.5 vs 6.4/0.59**	**NA/0.66**	**10.3 vs 4.7/0.54**	**0.52**

Clinical trial	**STORM**		**HORIZON**		**DREAMM-2**		**KARMMA-1**	
Population	ITT	High risk	ITT	High risk	ITT	High risk	ITT	High risk
Treatment	Sd	Sd	Melflufen-dex	Melflufen-dex	Belamaf	Belamaf	Ide-cel	Ide-cel
PFS (m)/HR	**3.7**	**3.3* and 4.6***	**4.2**	**3.0**	**3.9**	**2.1**	**8.8**	**10.4**

*High-risk definition: gene expression profiling high risk, t(14;16), t(14;20), del(17p), amp1q21, plasma cell leukemia, elevated serum LDH (2 × upper limit of normal).

Belamaf, belantamaf mafodotin; dex, dexamethasone; DKd, daratumumab, carfilzomib, and dexamethasone; DRd, daratumumab, lenalidomide, and dexamethasone; DRVd, daratumumab, lenalidomide, bortezomib, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; DVMP, daratumumab, bortezomib, melphalan, and prednisone; DVTd, daratumumab, bortezomib, thalidomide, and dexamethasone; Elo, elotuzumab; EloPd, elotuzumab, pomalidomide, and dexamethasone; EloRd, elotuzumab, lenalidomide, and dexamethasone; Ide-cel, idecabtagene vicleucel; IRd, ixazomib, lenalidomide, and dexamethasone; IsaKd, isatuximab, carfilzomib, and dexamethasone; IsaPd, isatuximab, pomalidomide, and dexamethasone; ITT, intention-to-treat population; Kd, carfilzomib and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; KRd-T, carfilzomib, lenalidomide, and dexamethasone followed by transplant; KRd 12, KRd for 12 cycles; m, months; NA, not available; NR, not reached; PVd, pomalidomide, bortezomib, and dexamethasone; Rd, lenalidomide and dexamethasone; RVd, lenalidomide, bortezomib, and dexamethasone; Sd, selinexor and dexamethasone; SVd, selinexor, bortezomib, and dexamethasone; VTd, bortezomib, thalidomide, and dexamethasone.

Management of high-risk patients with CAR-T cell therapy

BCMA is an attractive and extensively studied target for immunotherapy in MM. BCMA-targeting CAR-T cells have demonstrated fast, high, and deep responses in patients with RRMM. The sample sizes across the different trials are so far rather small but have included a great proportion of patients with high-risk features, such as high-risk CA, R-ISS III, EMD, or high tumor burden.[32,33] Idecel (idecabtagene vicleucel), indeed, already has been approved by US Food and Drug Administration for RRMM after at least 4 rounds of therapy, including PIs, immunomodulatory drugs, and anti-CD38, and has been evaluated in 128 patients with RRMM after a median of 6 prior lines (84% triple refractory). The ORR (overall response rate) was 73%, including a complete remission rate of 33% and a median PFS of 8.8 months. These efficacy data were sustained in patients with high-risk features, such as EMD (n = 50), high-risk CA (n = 45), or high tumor burden (n = 65)[34] (Table 2). Many other BCMA-targeted CAR-T cells are under investigation, and some clinical trials are focused in patients with high-risk features (Table 3). If results are positive, CAR-T cell therapy will rapidly move as the first choice in patients with high-risk features.

Beyond BCMA-targeted CAR-T cells, there are other therapeutic options, such as bispecific moABs targeting not only BCMA but also GPRC5D, FcRH5, and others, under evaluation in patients with RRMM, and their efficacy will be also evaluated in patients with high-risk features.

In summary, in 2021, the identification of high-risk patients with MM continues being an unmet medical need, and the definition should be revisited. Genomics will help us to improve the identification of these patients, as well as the therapeutic advances, to find the best option for them. Considering the achievement of undetectable and sustained MRD can abrogate the poor prognosis of high-risk features, the management of these patients should be response adapted and determined from exposition to sequential treatments based on drugs with a new and different mechanism of action. International effort and research in this regard are required.

Conflict-of-interest disclosure

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Off-label drug use

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