REVIEW ARTICLE

Translocation t(11;14) and BCL2-inhibition in multiple myeloma

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Abstract

Multiple myeloma is an increasingly treatable disease with improved survival, although characterized by multiple subclones that drive heterogeneity and variable clinical outcomes between patients. A biomarker-driven approach can help to tailor treatment and improve patient outcomes. Translocation t(11;14), a primary cytogenetic abnormality present in 15-20% of myeloma patients at diagnosis, is currently the most prominent targetable lesion in myeloma. In the era of induction with proteasome inhibitors and/or immunomodulatory drugs, t(11;14) has been associated with poorer outcomes compared to other standard-risk subgroups, with shorter progression-free and overall survival. The presence of t(11;14) in myeloma cells confers increased dependence on the pro-survival BCL2 protein, thus driving its ability to evade apoptosis, and is the main biomarker predicting response to BCL2-inhibitors. This review examines the pathogenesis and prognostic significance of t(11;14) in myeloma and the impact of concurrent high-risk cytogenetics, the mechanism of action of BCL2-inhibitors, cumulative evidence supporting their use, and proposed mechanisms of resistance. The review also presents potential future directions regarding BCL2-inhibitor-based regimens and how best to position these drugs to optimize patient outcomes.

Introduction

Multiple myeloma (MM) is an incurable hematologic malignancy. Recent advances, particularly in immune therapies (e.g., bispecific antibody-T cell engagers and chimeric antigen T-cell receptor therapy) and small molecules (e.g., BCL2-inhibitors, cereblon E3 ligase modulators), have significantly improved progression-free survival (PFS) and overall survival (OS). However, the treatment of MM remains challenging due to the significant heterogeneity, with variable treatment responses both between patients and across successive relapses. This has driven efforts to identify specific molecular targets in MM to allow for a biomarker-driven approach to treatment.[1] Currently, the only targetable lesion in MM is the t(11;14) translocation. Although not classified as a high-risk lesion in the Revised International Staging System (R-ISS)[2] for MM or the new International Myeloma Society (IMS) and International Myeloma Working Group (IMWG) Consensus Genomic Staging of high-risk MM,[3] there is growing evidence that patients with t(11;14) have poorer outcomes compared to standard-risk patients, with lower response to immunomodulatory drugs (IMiD), proteasome inhibitors (PI) and novel therapeutics – representing a population with unmet clinical needs.[4-8] MM cells with t(11;14) overexpress the pro-survival BCL2 protein, which makes them particularly susceptible to treatment with BCL2-inhibitors. This sensitivity has been confirmed in preclinical models, and demonstrated in clinical practice;[9-17] however, no BCL2-inhibitors have yet received regulatory approval for the treatment of myeloma.

This review delves into the prognostic implications of t(11;14) and the pathogenesis of BCL2 dependence. It also explores the current evidence supporting BCL2-inhibitor treatment in this subpopulation of patients as well as potential mechanisms of resistance, and in doing so informs our direction for future development of BCL2-inhibitor-based regimens.

Translocation t(11;14) in multiple myeloma

Chromosomal abnormalities play a critical role in the clonal evolution of plasma cells and drive disease emergence and progression. Genetic profiling is important in the risk

stratification and prognostication of MM patients; it informs our treatment algorithm as clinicians and allows for risk-adapted treatment. Chromosomal abnormalities in MM are classified into primary or secondary abnormalities. Primary abnormalities, usually translocations, such as t(4;14), t(11;14), and t(14;16), or trisomies, are present at diagnosis (i.e., initiating lesions), while secondary abnormalities, such as del(17p) and 1q gain/amplification (1q+), usually occur at disease relapse.

Incidence of t(11;14) in multiple myeloma

Primary aberrant *IGH* rearrangements occur in 60% of MM, with t(11;14) being the most common.[18] Historically, t(11;14) was thought to occur in only a small subset of patients, with a quoted incidence of 5% based on conventional karyotyping. However, conventional karyotyping has lower sensitivity due to low plasma cell proliferation.[19,20] With the use of interphase and cytoplasmic fluorescence *in situ* hybridization (FISH) testing, t(11;14) has been found to occur in 15-20% of MM patients.[21,22] In primary plasma cell leukemia, the incidence of t(11;14) is even higher, up to nearly 50%.[23-25] Higher prevalence of t(11;14) has also been reported in African-American patients,[26,27] although a more recent large prospective cohort study analyzing data from the Connect MM Registry demonstrated similar prevalence of t(11;14) by race.[28]

In some laboratories, the standard cytogenetics/FISH panel does not automatically include t(11;14) testing, resulting in under-reporting. However, given the known poorer prognosis of these patients as well as the targetable nature of this translocation, t(11;14) is now increasingly being incorporated as part of the diagnostic panel in patients with suspected MM. While cytogenetics/FISH testing is the standard method of detection for t(11;14), micro single nucleotide polymorphism-array or next-generation sequencing can also be used, although these tests are not as easily accessible. In countries in which next-generation sequencing testing is accessible, this is potentially a more cost-effective method of biomarker testing.

Pathogenesis of t(11;14) and BCL2-dependence in multiple myeloma

The survival of MM cells with t(11;14) is driven by their ability to evade cellular apoptosis. This ability is underpinned by overexpression of the pro-survival BCL2 protein. To understand the pathogenesis of t(11;14) MM, we first need to appreciate the critical role that the BCL2 family of proteins plays in regulating the intrinsic pathway of apoptosis and cell survival.

The BCL2 network consists of three functional subfamilies, that is, the anti-apoptotic/pro-survival members (e.g., BCL2, MCL1, BCL-XL), pro-apoptotic members (BAX and BAK), and BH3-only members (e.g., BIM, BID, BAD, NOXA).[29] Anti-apoptotic BCL2-proteins maintain cellular viability via inhibition of BAX and BAK. In response to physiological stressors, expression of BH3-only proteins is increased; these proteins bind pro-survival BCL2-proteins thus allowing for BAX/BAK-driven apoptosis (Figure 1A). In myeloma cells, the presence of t(11;14) confers an increased dependence on BCL2, with high levels of expression compared to the other anti-apoptotic proteins, BCL-XL and MCL1.[30] This dysregulated balance of pro-survival and pro-apoptotic proteins drives ongoing MM cell survival (Figure 1B).

Our understanding of this mitochondrial pathway of life-death has led to the development of small molecules that mimic BH3-only proteins. BH3-mimetics bind tightly to pro-survival BCL2-proteins, and inhibit their ability to bind to BAX/BAK (Figure 1C). Cancer cells that are particularly reliant on BCL2 are highly sensitive to these drugs. Venetoclax is a first-in-class oral BCL2-selective BH3-mimetic that has demonstrated efficacy in the treatment of various hematologic malignancies such as acute myeloid leukemia and chronic lymphocytic leukemia and has received approval for the treatment of these conditions.

In the MM space, a preclinical study by Touzeau *et al.*[9] confirmed that myeloma cell lines with *CCND1* translocation were the most sensitive to venetoclax, with a high BCL2/MCL ratio being the most powerful biomarker for predicting sensitivity to venetoclax. This has successfully translated into clinical practice with multiple studies demonstrating the efficacy of venetoclax, as well as second-generation BCL2-inhibitors, in the treatment of relapsed and/or refractory MM (RRMM) patients with t(11;14).[10-17,31,32]

It is important to note, however, that BCL2-protein overexpression with high BCL2/BCL-XL or BCL2/MCL1 ratio is not synonymous with the presence of t(11;14). This was demonstrated by De Ramon *et al.*[33] in an analysis of 120 patients with newly diagnosed MM (NDMM) treated on the PETHEMA/GEM2012 study. Quantification of BCL2-family protein expression was performed on patient samples using capillary nanoimmunoassay. While t(11;14) patients had significantly higher BCL2/BCL-XL ratios compared to non-t(11;14) patients, some patients with other cytogenetic abnormalities expressed a higher ratio compared to those of the third quartile of the t(11;14) cohort. Certainly, the efficacy of venetoclax has also been demonstrated in non-t(11;14) myeloma with high BCL2 expression in both *in vitro* and clinical studies.[33-35] This suggests that quantification of BCL2-protein expression could potentially be a better and more inclusive biomarker predicting response to BCL2-inhibitor therapy, rather than relying solely on the presence of t(11;14). BCL2-protein expression in MM patients has been analyzed via RNA sequencing, immunohistochemistry, and flow cytometry.[35-38] There is yet, however, to be a standardized method of BCL2 quantification, thus making t(11;14) translocation currently the main biomarker for response to BCL2-inhibitors.

Prognostic implications of t(11;14) in multiple myeloma

Based on the R-ISS staging system[2] and the recently pub-

lished IMS/IMWG Consensus Genomic Staging of high-risk MM,[3] isolated t(11;14) is still considered a standard-risk lesion. However, there is now growing consensus that t(11;14) does confer inferior prognosis, with poorer outcomes compared to other standard-risk subgroups.

Several studies have reported on the impact of t(11;14) on patient outcomes.[4-8,21,22,28] Results of clinical studies on NDMM patients treated with conventional chemotherapy concluded t(11;14) to be a neutral genetic lesion.[21,22] However, studies in the era of induction with IMiD and/or PI demonstrate that patients with t(11;14) and no other high-risk chromosomal abnormality have shorter PFS, OS and time to next treatment.[4-8] Table 1 provides a detailed summary of these studies.

In the largest study to date investigating t(11;14) patients, Bal *et al.*[6] compared a total of 5,581 patients across five cohorts: del(17p) *versus* high-risk chromosomal abnormality *versus* chromosome 1 abnormality *versus* t(11;14) with no high-risk lesions *versus* non-t(11;14). This robust study provided a nuanced analysis not just of the significance of t(11;14), but also provided insight into its behavior in the presence of other cytogenetic abnormalities. Patients with t(11;14) had shorter PFS compared to the non-t(11;14) group, but longer PFS compared to the other three groups. There was no difference in PFS or OS between the t(11;14) and non-t(11;14) group who had combination IMiD and PI induction. Survival in t(11;14) patients with concomitant chromosome 1 abnormality was similar. However, patients with t(11;14) and del(17p) had worse OS compared to patients with del(17p) without *IGH* translocations (34 months *vs*. 47 months, $P<0.01$), suggestive of a "double-hit" phenomenon. This is consistent with the findings of a retrospective study at Mayo Clinic of 795 NDMM patients in whom the presence of concurrent del(17p) (10.7%) and ISS stage III were predictive of reduced OS in the t(11;14) cohort.[5]

One study in the era of IMiD and/or PI induction found

Table 1. Summary of key studies on t(11;14) in newly diagnosed multiple myeloma.

Studies	Cohorts	N	Results			Study details	Main findings
			3-year PFS	mPFS	3-year OS		
Sasaki *et al.*, 2013[4]	Normal CG	869	47%	33 mths	83%	Retrospective study. 67% patients received IMiD-based or PI-based induction.	After ASCT, patients with t(11;14) had worse outcomes than patients with normal CG, but better than those with HRCA.
	t(11;14)	27	27%	23 mths	63%		
	HRCA†	97	13%	9.7 mths	34%		
			P<0.00001	*P*<0.00001	*P*<0.00001		
			mPFS	**mTTNT**	**mOS**	**mOS excluding del(17p)**	
Lakshman *et al.*, 2018[5]	t(11;14)	65	23 mths	20.8 mths	74.4 mths	81.7 mths	Retrospective study. Induction regimen: IMiD+PI: 14.9%; PI-based: 32.6%; IMiD-based: 45.5%.	Patients with t(11;14) had worse outcomes than the no-translocation group, but better outcomes than patients with high-risk translocations. Del(17p) and ISS stage III predicted worse OS among patients with t(11;14). With del(17p), OS was similar between the t(11;14) and no-translocation group.
	Non-(11;14) translocations	132	19 mths	18.2 mths	49.8 mths	58.2 mths		
	No translocations	598	28.3 mths	27 mths	103.6 mths	108.3 mths		
			P<0.01	*P*=0.01	*P*<0.01	*P*<0.01		
			Post-VRd induction ≥VGPR rate	**mPFS**				
Kaufman *et al.*, 2018[8]	t(11;14)	122	49.5%	51 mths			Retrospective study. All patients received IMiD+PI with VRd.	Patients with t(11;14) had poorer outcomes than standard-risk patients.
	Standard risk (i.e., no del(17p), t(4;14), t(14;16) or complex karyotype)	527	76.3%	75 mths				
			P<0.001	*P*<0.001				

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Studies	Cohorts	N	Results			Study details	Main findings
			mPFS				
Bal *et al.*, 2021[6]	Del(17p)	544	[Worse PFS compared to t(11;14)]			Retrospective study. Induction regimen: IMiD+PI: 43.6%; PI-based: 28.8%; IMiD-based: 17.4%.	Patients with t(11;14) had poorer outcomes compared to the non-t(11;14) group, but better than the group with HRCA. No PFS/OS differences between patients with t(11;14) or non-t(11;14) with IMiD+PI induction. Patients with t(11;14) + del(17p) had worse OS than those with del(17p) alone (34 mths *vs.* 47 mths, *P*<0.01).
	HRCA††	415					
	Chr(1) abnormality	1,124					
	t(11;14) with no high-risk lesions	589	36.1 mths				
	Non-t(11;14)	2,909	40.1 mths				
			P=0.03				
			mPFS	**mOS**			
Gasparetto *et al.*, 2022[28]	t(11;14)	378	34.8 mths	74 mths		Multicenter prospective cohort study. Induction regimen: IMiD+PI: 34.7%; PI-based: 40%; IMiD-based: 12.8%.	t(11;14) was a neutral prognostic factor regardless of induction type.
	Non-t(11;14)	1,196	35.7 mths	77.3 mths			
			P=0.77	*P*=0.94			
			mPFS1	**mPFS2**	**mOS**		
Lim *et al.*, 2023[7]	t(11;14)	74	22.1 mths	8.2 mths	64.2 mths	Retrospective study. Induction regimen: IMiD+PI: 0%; PI-based: 81%; IMiD-based: 14%.	No PFS1 difference, but PFS2 shorter in the t(11;14) group than in the hyperdiploid group.
	Hyperdiploid without translocations	111	27.9 mths	19.8 mths	100.9 mths		
	High-risk *IGH* translocations	159	26.7 mths	10.0 mths	59.0 mths		
			P=0.503	*P*=0.002	*P*=0.055		

†del(13q), hypodiploidy, t(4;14), t(14;16), t(14;20), or del(17p); ††t(4;14), t(14;16) or t(14;20). PFS: progression-free survival; m: median; OS: overall survival; CG: cytogenetics; HRCA: high-risk chromosomal abnormalities; mths: months; IMiD: immunomodulatory drug; PI: proteasome inhibitor; ASCT: autologous stem cell transplant; TTNT: time to next treatment; ISS: International Staging System; VRd: bortezomib, lenalidomide and dexamethasone; VGPR: very good partial response; PFS1: first PFS; PFS2: second PFS.

t(11;14) to be a neutral prognostic factor. The Connect MM Registry was a large prospective study that showed that the presence of t(11;14) had no impact on PFS or OS, regardless of the type of induction therapy.[28] The authors concluded that concurrent cytogenetic abnormalities were more important to consider when evaluating the prognostic impact of t(11;14). It is important to note, however, that only a third of patients in this study received combination IMiD and PI induction.

The study that is most applicable to current clinical practice is a retrospective study by Kaufman *et al.*[8] of 1,000 NDMM patients who all had induction with combination IMiD and PI (lenalidomide-bortezomib-dexamethasone). Patients with t(11;14) had lower rates of very good partial response or better after induction (49.5% *vs.* 76.3%, *P*<0.001), and shorter median PFS (51 months *vs.* 75 months, *P*<0.001) compared to those with standard-risk cytogenetics. This difference was even more marked in patients who did not receive maintenance therapy. The impact of t(11;14) on outcomes in patients who underwent autologous stem cell transplant (ASCT) at MD Anderson was evaluated in a retrospective study on which two-thirds of patients received induction with IMiD and/or PI.[4] Patients with t(11;14) had shorter PFS and OS compared to the cohort with normal cytogenetics, but better outcomes compared to those with high-risk chromosomal abnormalities. The recently presented phase III MIDAS study evaluated a minimal residual disease (MRD)-driven consolidation and maintenance approach following induction of all NDMM patients with quadruplet therapy of isatuximab, carfilzomib, lenalidomide and dexamethasone.[39] The NDMM patients with t(11;14) demonstrated lower MRD negativity rates after induction and consolidation compared to those who did not have t(11;14), at 40% *versus* 59% and 63% *versus* 78%, respectively. Results from the Mayo Clinic support early ASCT in t(11;14) patients; patients with t(11;14) had a shorter estimated OS compared to that of the group without the translocation (74.4 months *vs.* 103.6 months, *P*=0.003), with early ASCT

demonstrated to improve OS in all cohorts.[5] In the t(11;14) cohort, the median OS with early ASCT was 88.4 months, compared to 58.1 months for those undergoing delayed ASCT (*P*=0.002).

Overall, cumulative evidence strongly suggests that t(11;14) confers a poorer prognosis compared to that of other standard-risk subgroups. It is also vital to consider coexisting cytogenetic lesions when evaluating the prognostic power of t(11;14), particularly the presence of del(17p) and 1q+. This can help to predict response to therapy both at diagnosis as well as at relapse. Concurrent del(17p) and/or 1q+ portends poorer outcomes in all MM patients, but also appears to reduce sensitivity to treatment with BCL2-inhibition in t(11;14) patients. In a retrospective study of 232 RRMM patients treated at the Mayo Clinic with venetoclax-based regimens, 37/190 (19.5%) and 64/190 (33.7%) of t(11;14) patients had concurrent del(17p) and 1q+, respectively. The t(11;14) patients with either of these cytogenetic abnormalities had lower overall response rates (ORR) (57% *vs*. 71%, *P*=0.04) and significantly shorter median PFS (7.7 months *vs*. 15.1 months, *P*=0.013) when compared to those with no abnormalities.[40] The findings of these studies bring to the forefront the importance of utilizing highly effective treatments in the treatment of t(11;14) patients early in the disease course, prior to the development of secondary cytogenetic lesions that confer an even poorer prognosis. The question of the optimal BCL2-inhibitor combination regimen in this subpopulation of patients with t(11;14) and concurrent high-risk cytogenetics remains unanswered.

Targeted therapy in the treatment of t(11;14) multiple myeloma

Currently, translocation t(11;14) is the only targetable lesion in MM. Given this, as well as the fact that patients with this translocation have worse outcomes compared to those with standard-risk MM, the use of BCL2-inhibition as a preferred therapeutic strategy in this cohort of patients is of particular interest. To date, no BCL2-inhibitors have received regulatory approval for the treatment of MM. Despite the fact that BCL2-inhibitors are not yet licensed, the current international recommendation for t(11;14) patients with relapsed disease is to use a BCL2-inhibitor-based regimen, where accessible.[41,42]

Venetoclax

A BCL2-inhibitor was first investigated for use in MM in a phase I study in which RRMM patients were treated with venetoclax monotherapy at doses up to 1,200 mg daily.[10] The ORR was 21% (14/66) in all patients, with a higher ORR of 40% (12/30) demonstrated in the subset with t(11;14). The t(11;14) subgroup was heavily pre-treated with a median of five prior lines of therapy (range, 1-10); 77% of patients were lenalidomide-refractory and 67% were double-class refractory to two classes of drugs.

A subsequent phase I/II study by Kaufman *et al.*[11] investigated the combination of venetoclax and dexamethasone specifically in RRMM patients with t(11;14). The phase II portion of this study included 31 patients who had received a median of five (range, 2-12) prior lines of therapy, with the majority of patients being refractory to IMiD, PI and/or daratumumab. Doublet therapy produced an encouraging ORR of 48%, with 36% of patients achieving a very good partial response or better. The median time to progression was 10.8 months. Exploratory studies also confirmed that higher BCL2 levels were seen in patients who achieved a partial response or better, consistent with our understanding of the mechanism of action of BCL2-inhibitors in t(11;14) MM. The positive results of this study also support *in vitro* findings by Matulis *et al.*[43] regarding the synergistic effect of venetoclax and dexamethasone. In MM cell lines, dexamethasone shifts BIM binding towards BCL2, resulting in increased sensitivity to venetoclax and hence increased cell death.

Clinical studies on venetoclax combination treatments

A number of studies have since explored the use of venetoclax and dexamethasone in combination with other standard-of-care drugs, including bortezomib, daratumumab and carfilzomib, with clinical evidence of synergism.[12-16,34] These studies are summarized in Table 2.

The phase III BELLINI study investigated the addition of venetoclax to bortezomib and dexamethasone in RRMM patients who had been treated with one to three prior lines of therapy.[12,13,34,44] This study included both non-t(11;14) (N=256) and t(11;14) patients (N=35), and demonstrated significant improvement in PFS across all patients with venetoclax *versus* placebo plus bortezomib and dexamethasone (median PFS 23.4 months *vs*. 11.4 months; hazard ratio [HR]=0.58). The positive effect of venetoclax on patient outcomes was particularly evident in the subgroup of patients with t(11;14) and/or high BCL2 expression.[45] Interestingly, of the patients who were t(11;14)-positive, 45.7% (16/35) did not have high BCL2 expression. A total of 98 patients had high BCL2 expression, of whom the majority (80.6%; 79/98) did not have t(11;14). In the t(11;14) cohort, the median PFS was 36.8 months in the venetoclax arm *versus* 9.3 months in the placebo arm (HR=0.17). Similarly, the patients with high BCL2 expression had significantly longer PFS with the addition of venetoclax (30.1 months *vs*. 9.9 months; HR=0.36). In the recently published final survival results, at a median follow-up of 45.6 months, OS in the t(11;14) subgroup was not reached in either treatment group.[44] Conversely, OS was in favor of the placebo group in the subgroup without t(11;14) and with low BCL2 expression (median OS 46.1 months with venetoclax *vs*. not reached with placebo; HR=1.38). Another critical finding of the BELLINI study was that of increased rates of grade ≥3 infections in the venetoclax group, with an increased pro-

Table 2. Summary of published studies on BCL2-inhibitor-based regimens in patients with relapsed and/or refractory multiple myeloma.

Study	Regimen	N of patients	Efficacy results in t(11;14) patients†	Safety results across all patients
Kaufman *et al.*, 2021[11] Phase I/II	Ven 800 mg + Dex	All with t(11;14) Phase I = 20 Phase II = 31	Phase I: ORR 60% Phase II: ORR 48%	Neutropenia: 18% (≥G3: 10%) Thrombocytopenia: 18% (≥G3: 10%) Diarrhea: 35% Nausea: 28% RTI: 30% Sepsis: 8%
Kumar *et al.*, 2021 (BELLINI)[12,13,34,44] Phase III	Ven 800 mg + Vd *vs.* Vd	Total = 291 t(11;14) = 35 Non-t(11;14) = 256 Biomarker subsets: BCL2 high = 98 t(11;14) and/or BCL2 high = 114	Median follow-up: 45.6 mths mPFS: 36.8 mths *vs.* 9.3 mths (HR=0.17; *P*=0.00041) mOS: NR (NE-NE) *vs.* NR (43.6 mths-NE) (HR=0.77; *P*=0.47) In BCL2-high subset: mPFS 30.1 mths *vs.* 9.9 mths (HR=0.36; *P*=0.00014)	AE for VenVd *vs.* Vd: ≥G3 Neutropenia: 31% *vs.* 8% ≥G3 Thrombocytopenia: 26% *vs.* 40% ≥G3 Infections: 42% *vs.* 29% Pneumonia: 31% *vs.* 21% Fatigue: 33% *vs.* 32% Diarrhea: 60% *vs.* 50% Constipation: 36% *vs.* 31%
Bahlis *et al.*, 2021[16] Phase I	Part 1: Ven (400 mg or 800 mg) + Dd Part 2: VenDVd	Part 1: N=24; all with t(11;14) Part 2: N=24 t(11;14) = 6 Non-t(11;14) = 18	Part 1: ORR 95.8% ≥VGPR 95.8% 24m PFS: 90.8% Part 2: ORR: 91.7% ≥VGPR: 79.1% 24-mth PFS: not reported for t(11;14) patients (66.7% for all patients)	AE for VenDVd Neutropenia: 17% (≥G3 4%) Thrombocytopenia: 21% (≥G3 17%) Fatigue: 25% Diarrhea: 54% Nausea 50% Upper RTI: 21% Pneumonia: 4%
Costa *et al.*, 2021[15] Phase II	Ven (400 mg or 800 mg) + Kd	Total = 49 t(11;14) = 13 Non-t(11;14) = 36	ORR: 92% ≥VGPR: 85% Median duration of response: not reached (at a median follow-up of 27 mths)	Neutropenia: 22% (≥G3 12%) Thrombocytopenia: 31% (≥G3 8%) Diarrhea: 65% (≥G3 10%) Nausea: 47% (≥G3 4%) Upper RTI: 39% (≥G3 0%) Sinusitis: 20% (≥G3 0%) Pneumonia: 18% (≥G3 12%) Influenza: 16% (≥G3 6%)
Gasparetto *et al.*, 2021[52] Phase II	Ven 400 mg + PomDex	Total = 8 t(11;14) = 3 Non-t(11;14) = 5	Study terminated early due to concerns regarding AE. Decision to pursue biomarker-driven strategy. All patients had a ≥G3 adverse event, mainly neutropenia.	Neutropenia G3/4: 75%
Bahlis *et al.*, 2023[17] Phase I/II	Ven (400 mg or 800 mg) + Dd *vs.* DVd	All with t(11;14) Ven (400 mg)Dd = 26 Ven (800 mg)Dd = 29 DVd = 26	ORR: 96% *vs.* 65% ≥VGPR: 93% *vs.* 39% 33-month PFS: 73.4% *vs.* 38.8% MRD-negative rates: 38% *vs.* 8% (consistent across subgroups including lenalidomide refractory status and high-risk CG)	AE for VenDd:[70] ≥G3 neutropenia: 12.7% ≥G3 thrombocytopenia: 3.6% ≥G3 infections: 34.5% ≥G3 diarrhea: 7.8%
Mateos *et al.*, 2023[46] (CANOVA) Phase III	Ven 800 mg + Dex *vs.* PomDex	All with t(11;14) VenDex = 133 PomDex = 130	ORR: 62% *vs.* 35% (*P*<0.001) mPFS: 9.9 mths *vs.* 5.8 mths (*P*=0.237) *Post-hoc* analysis including censored patients – mPFS: 9.4 mths *vs.* 4.0 mths (HR=0.651; *P*=0.003)	AE for VenDex: ≥G3 neutropenia: 19% ≥G3 thrombocytopenia: 13% ≥G3 anemia: 13% ≥G3 infections: 22% (all grade 61%) ≥G3 diarrhea: 4%
Dhakal *et al.*, 2024[32,50] Phase Ib/II	Sonrotoclax 640 mg + Dex	All with t(11;14) N=24	ORR: 80.6% ≥VGPR: 55.6%	≥G3 Neutropenia: 14% ≥G3 Thrombocytopenia: 11% Infection: 72% (≥G3: 11%) Fatigue: 30.6% Diarrhea: 38.9% Nausea: 19.4% Constipation: 16.7%

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†Note that some studies included all-comers, i.e., both patients with t(11;14) and without t(11;14). The efficacy data presented in this table are only those reported for the cohorts of patients with t(11;14). Ven: venetoclax; Dex: dexamethasone; ORR: overall response rate; ≥G3: grade 3, 4 or 5 adverse event as per the Common Terminology Criteria for Adverse Events; RTI: respiratory tract infection; Vd: bortezomib and dexamethasone; BCL2 high: high expression of BCL2; PFS: progression-free survival; HR: hazard ratio; OS: overall survival; NR: not reached; NE: not estimable; AE: adverse events; Dd: daratumumab and dexamethasone; DVd: daratumumab, bortezomib and dexamethasone; VGPR: very good partial response; Kd: carfilzomib and dexamethasone; PomDex: pomalidomide and dexamethasone.

portion of infection-related deaths. In the subgroup with t(11;14) and/or high BCL2 expression, this was in keeping with longer duration of venetoclax exposure, and rates were within the expected range for the RRMM setting. However, in the non-t(11;14) and low BCL2 expression subgroup, higher infection rates were seen despite the patients being on treatment with venetoclax for a shorter time than on placebo; this was likely secondary to suboptimal disease control in these patients, together with venetoclax-induced immunosuppression. The BELLINI study concluded an overall favorable benefit-risk profile of venetoclax in patients with t(11;14) and/or high BCL2 expression.[44] These results have been crucial in informing the landscape of future studies on BCL2-inhibitors and the importance of a biomarker-driven approach in the selection of patients. They also highlight the importance of adequate anti-microbial prophylaxis when using BCL2-inhibitor-based regimens to reduce the risk of serious infections.

A recently published update of a phase I/II study comparing venetoclax *versus* bortezomib in combination with daratumumab and dexamethasone in 80 patients with t(11;14) who had been treated with one or more prior lines of therapy again demonstrated a significantly higher ORR (96.4% *vs*. 65.4%) with the use of venetoclax.[17] Responses were also significantly deeper in the venetoclax, daratumumab, dexamethasone arm with MRD-negativity rates of 38% *versus* 8% in the arm treated with bortezomib, daratumumab, and dexamethasone. This finding was consistent across all key subgroups of patients including those with high-risk cytogenetics and lenalidomide-refractory status. This translated into longer PFS in the venetoclax cohort with a 33-month PFS rate of 73.4% in the venetoclax, daratumumab, and dexamethasone cohort, *versus* 38.8% in the cohort treated with bortezomib, daratumumab, and dexamethasone.

The CANOVA study, designed to be a phase III registration level study, compared venetoclax and dexamethasone *versus* pomalidomide and dexamethasone in 263 patients with t(11;14)-positive RRMM who had received two or more prior lines of therapy. In the first read-out of this study, the venetoclax and dexamethasone combination was associated with a higher ORR of 63% *versus* 35% among patients treated with pomalidomide and dexamethasone (P<0.001).[46] However, while PFS was longer in the venetoclax and dexamethasone arm (9.9 months *vs*. 5.8 months), this did not reach statistical significance and the study did not meet its primary endpoint. This was likely due to informative censoring.[47] On reviewing the data, investigators found that 21 patients in the pomalidomide and dexamethasone arm, *versus* four patients in the venetoclax and dexamethasone arm, discontinued treatment for reasons other than disease progression or adverse events; these patients were censored in the primary PFS analysis. In the *post-hoc* PFS analysis, in which censored patients were included and in which the start of a new anti-myeloma therapy was accounted for as an event, investigators demonstrated a significantly longer PFS of 9.4 months *versus* 4.0 months for venetoclax and dexamethasone *versus* pomalidomide and dexamethasone (HR=0.651, P=0.003). The findings of the CANOVA study emphasize the importance of ensuring a study is sufficiently powered to account for informed censorship.

Second-generation BCL2-inhibitors

Despite the preliminary results of the CANOVA study, current cumulative evidence, including that of real-world data,[48,49] remains in strong support of the use of BCL2-inhibitors in the treatment of t(11;14) MM patients. Second-generation BCL2-inhibitors are now being explored.

Early data on sonrotoclax, a second-generation BH3-mimetic that binds and inhibits BCL2 with a potency more than 10 times that of venetoclax, has shown promising efficacy in the relapsed/refractory setting.[31] At a recommended phase II dose of 640 mg daily and in combination with dexamethasone, sonrotoclax has been found to be safe and tolerable and able to induce deep responses with ORR of 80.6% and a rate of very good partial response or better of 55.6% in heavily pre-treated patients (median prior lines of therapy, 3; range, 1-12).[32,50] This study is ongoing, with sonrotoclax currently being investigated in combination with other standard-of-care drugs including daratumumab and carfilzomib. ABBV-453 (surzetoclax) is another highly potent second-generation BCL2-inhibitor that has demonstrated high affinity and selectivity for BCL2 over BCL-XL and MCL1 with superior activity in xenograft models compared to other BCL2-inhibitors,[51] and is currently being investigated in combination with dexamethasone, daratumumab and lenalidomide. Table 3 summarizes ongoing clinical trials of venetoclax and second-generation BCL2-inhibitors.

Safety profile of BCL2-inhibitors

BCL2-inhibitors are also tolerable with an acceptable safety profile. The most common grade 3 or 4 hematologic adverse events observed are neutropenia and thrombocytopenia. Careful study design and risk management should be considered when combining BCL2-inhibitors with drugs that have

Table 3. Current ongoing recruiting clinical trials with BCL2-inhibitor based regimens.

BCL2-inhibitor	Phase of study	Patient population	Regimens	Clinical Trial ID
Venetoclax	Phase Ib/II	t(11;14) RRMM	Venetoclax + Iberdomide + Dexamethasone	ACTRN12622001158752
	Phase I	t(11;14) NDMM (TIE)	Venetoclax + Daratumumab + Dexamethasone Venetoclax + Lenalidomide + Dexamethasone Venetoclax + Daratumumab + Lenalidomide + Dexamethasone	NCT06042725
		t(11;14) RRMM	Venetoclax + Lenalidomide + Dexamethasone Venetoclax + Daratumumab + Lenalidomide + Dexamethasone	
	Phase II	t(11;14) RRMM	Venetoclax + Selinexor + Dexamethasone	NCT05530421
	Phase I	t(11;14) RRMM	Venetoclax + Tocilizumab	NCT05391750
	Phase II	t(11;14) RRMM	Venetoclax + Isatuximab + Dexamethasone	NCT06115135
	Phase I/II	t(11;14) RRMM	Venetoclax + Belantamab mafadotin +/- Dexamethasone	NCT05853965
Sonrotoclax	Phase Ib/II	t(11;14) RRMM	Sonrotoclax monotherapy Sonrotoclax + Dexamethasone Sonrotoclax + Carfilzomib + Dexamethasone Sonrotoclax + Daratumumab + Dexamethasone Sonrotoclax + Pomalidomide + Dexamethasone	NCT04973605
Surzetoclax (ABBV-453)	Phase I	RRMM with t(11;14) and/or BCL2 high	Surzetoclax monotherapy Surzetoclax + Dexamethasone Surzetoclax + Daratumumab + Dexamethasone Surzetoclax + Daratumumab + Lenalidomide + Dexamethasone	NCT05308654
	Phase I/II	RRMM with t(11;14) and/or BCL2 high	Surzetoclax monotherapy Surzetoclax + Daratumumab + Dexamethasone	NCT06953960
Lisaftoclax (APG-2575)	Phase Ib/II	RRMM with or without t(11;14)	Lisaftoclax monotherapy Lisaftoclax + Lenalidomide + Dexamethasone	NCT04674514
	Phase Ib/II	RRMM with or without t(11;14)	Lisaftoclax + Pomalidomide + Dexamethasone Lisaftoclax + Daratumumab + Lenalidomide + Dexamethasone	NCT04942067

ID: identity; RRMM: relapsed and/or refractory multiple myeloma; NDMM: newly diagnosed multiple myeloma; TIE: transplant ineligible; BCL2 high: high expression of BCL2.

overlapping hematologic toxicities. A phase II study investigating venetoclax with pomalidomide and dexamethasone was terminated early because all patients experienced a grade ≥3 adverse event, most commonly neutropenia (75%; 6/8 patients).[52] However, only three out of eight patients in this study had t(11;14). This study again highlights the importance of a biomarker-driven approach. There is currently an active study investigating a novel combination of venetoclax with iberdomide (cereblon E3 ligase modulator) and dexamethasone, specifically in t(11;14) patients with one to two prior lines of therapy (ACTRN12622001158752).

Common non-hematologic adverse events include infections and gastrointestinal symptoms, particularly diarrhea.[53] As highlighted in the BELLINI study, infections remain one of the most serious non-hematologic adverse events with the use of BCL2-inhibitors.[44] In a recently published real-world retrospective analysis of t(11;14) RRMM patients from nine French centers treated with venetoclax-based therapies (N=46), there was a 24% incidence of grade ≥3 infections.[49] Of the 18 patients who died, two did so of infections. The majority of patients were reported to be on prophylaxis against *Pneumocystis jirovecii* pneumonia and herpes simplex virus (95% and 96%, respectively), while only 11% received immunoglobulin replacement therapy. Encouragingly, early data from studies on sonrotoclax 640 mg and dexamethasone have shown lower rates of severe infections; rates of grade 3/4 neutropenia and grade 3/4 infections were only 14% and 11%, respectively.[32,50]

Mechanisms of resistance to BCL2-inhibitors

Our understanding of the mechanisms of resistance to BCL2-inhibitors in MM remains limited, and much of our current knowledge is that gained from work done in acute

myeloid leukemia and lymphoid malignancies.[54-56] Acquired resistance has been reported to occur secondary to over-expression of non-BCL2 anti-apoptotic proteins (MCL1 and BCL-XL),[57-60] acquired mutations in BCL2,[61-63] and alterations in mitochondrial metabolism[64] (Figure 1D).

The upregulation of MCL1 is a key mechanism of resistance that has been identified. In the presence of BCL2-inhibitors, increased MCL1 sequesters BH3-only proteins that have been released from BCL2, thus preserving mitochondrial metabolism and cell survival. In acute myeloid leukemia and lymphoid cell lines, concurrent treatment with MCL1-inhibition resulted in restoration of venetoclax sensitivity.[57-60] In myeloma, upregulation of non-BCL2 anti-apoptotic proteins has been linked to copy number amplification of 1q21 and changes in the bone marrow microenvironment.[65-68] Human myeloma cell lines with co-expression of BCL2 and BCL-XL have been shown to be resistant to venetoclax, but sensitive to a BCL-XL-selective inhibitor. In xenograft models, co-expression of BCL2 and MCL1 also resulted in venetoclax resistance; this was circumvented by co-treatment with bortezomib, as the latter upregulates the pro-apoptotic factor NOXA, which functions to neutralize MCL1.[36]

BCL2 BH3-binding groove mutations, such as Gly101Val and Asp104Tyr, reduce the affinity of BCL2-inhibitors and are also a recognized mechanism of resistance.[61-63] In chronic lymphocytic leukemia cells, Gly101Val has been demonstrated to reduce the affinity of venetoclax to BCL2 by approximately 180-fold, thus preventing the displacement of BIM/BAX from BCL2.[61]

The pathogenesis of acquired resistance to BCL2-inhibitors is complex and diverse. It is also likely that there are independent mechanisms at play in individual malignant subclones.[54] This is particularly pertinent in MM given that this is an intrinsically heterogeneous disease with multiple

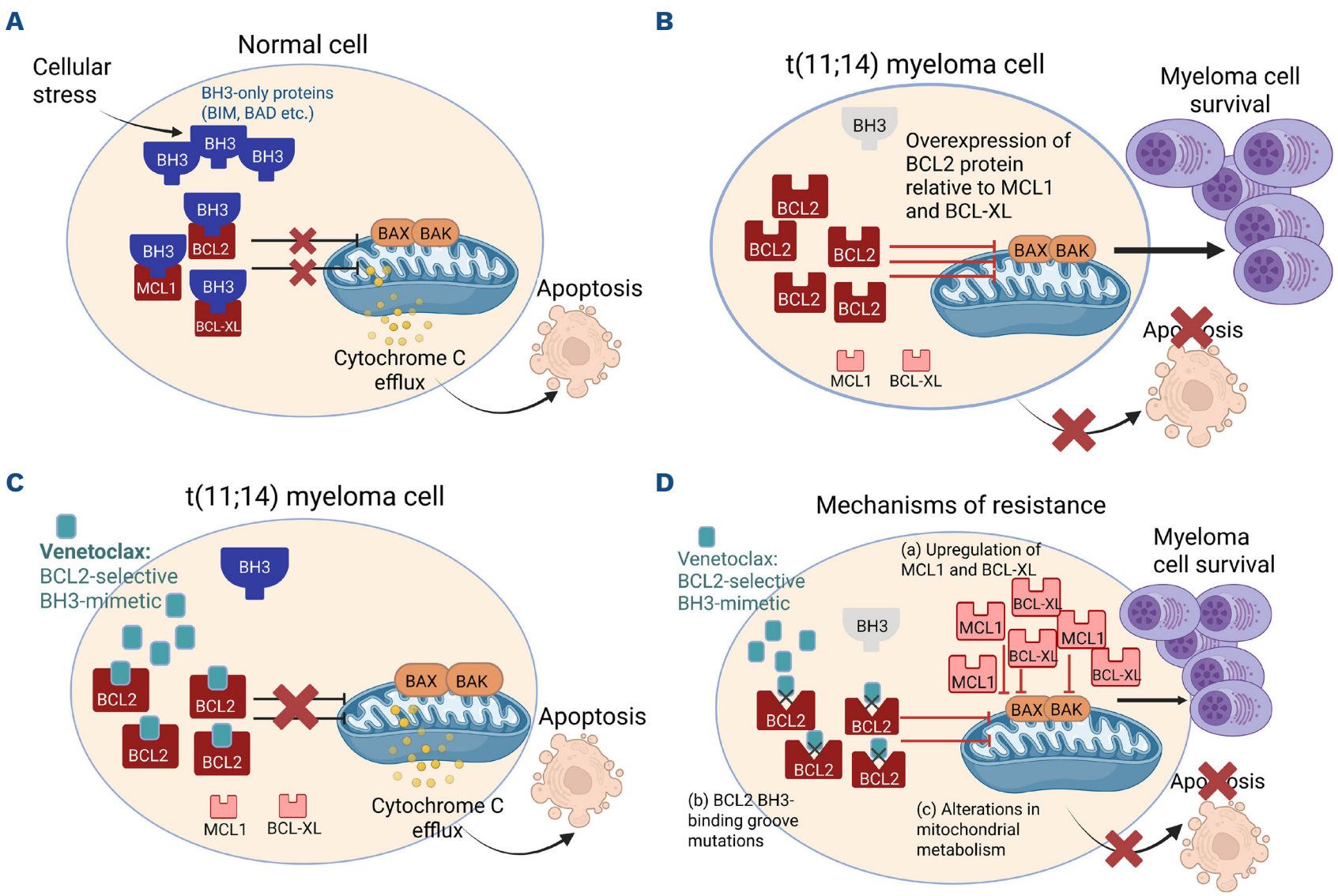

Figure 1. BCL2 protein family-driven regulation of cellular survival and apoptosis: dysregulation in t(11;14) myeloma cells, mechanism of action of BH3-mimetics and potential mechanisms of resistance. (A) Regulation of the intrinsic apoptotic pathway by the BCL2 family of proteins in normal cells. In response to physiological stressors, expression of BH3-only proteins is increased. These proteins bind and inhibit pro-survival BCL2 proteins, thus allowing for BAX/BAK-driven apoptosis. (B) The presence of t(11;14) in myeloma cells confers an increased dependence on BCL2, with high levels of expression compared to the other anti-apoptotic proteins, BCL-XL and MCL1. This dysregulated balance of pro-survival and pro-apoptotic proteins drives ongoing survival of multiple myeloma cells. (C) Venetoclax is a first-in-class oral BCL2-selective BH3-mimetic that binds tightly to pro-survival BCL2 proteins and inhibits their ability to bind to BAX/BAK, thus allowing cellular apoptosis. (D) Acquired resistance has been reported to occur secondary to (a) upregulation of non-BCL2 anti-apoptotic proteins (MCL1 and BCL-XL), (b) acquired BCL2 BH3-binding groove mutations, and (c) alterations in mitochondrial metabolism. Figure created in BioRender.com.

subclones. More work is required to understand resistance to BCL2-inhibitors in MM, to allow for mechanistically rational combination treatments and/or the development of new drugs that can overcome resistance.

Future of BCL2-inhibitor therapy in t(11;14) multiple myeloma

As we work towards regulatory approval of BCL2-inhibitors, there are many ongoing key questions to be addressed by future clinical studies. These include incorporation of BCL2-inhibitors into induction therapy for NDMM t(11;14) patients, examination of the role of BCL2-inhibitors in the era of T-cell engager therapies, establishment of a standardized and accessible method of BCL2-protein quantification, and further investigation of mechanisms of resistance to BCL2-inhibitors in MM.

All patients should be screened for t(11;14) at diagnosis, to enable early access to BCL2-inhibitor-based combination treatment, before the disease becomes more resistant via the acquisition of high-risk secondary mutations at relapse, such as del(17p) and 1q+.[40] Indeed, a recent meta-analysis by Xu *et al.*[53] demonstrated higher response rates to venetoclax in patients who were less heavily pre-treated. Considering this, and the fact that t(11;14) is associated with suboptimal responses to IMiD- and PI-based induction therapies (as outlined in Table 1), BCL2-inhibitor combination treatments warrant investigation in the newly diagnosed setting. Such studies should also include patients with primary plasma cell leukemia, in whom t(11;14) occurs in nearly 50% of cases and prognosis remains dismal.[23-25] Patients with t(11;14) may benefit from a different treatment approach, including incorporating a BCL2-inhibitor at the outset. This strategy is rational, as t(11;14) is present in all subclones, and early intervention with a BCL2-inhibitor could effectively target the entire myeloma clone population. Currently, there is a phase I study testing the safety and efficacy of combination venetoclax with lenalidomide-dexamethasone, daratumumab-dexamethasone, and daratumumab-lenalidomide-dexamethasone in NDMM transplant-ineligible patients with t(11;14) (NCT06042725), but not in transplant-eligible patients. The incorporation of BCL2-inhibition into the induction phase, as well its role in maintenance after ASCT with or without lenalidomide, would be an area of interest for future studies.

Perhaps the most exciting key area for exploration is the role and sequencing of BCL2-inhibitor therapy in the era of T-cell engager therapies (e.g., bispecific or trispecific antibodies, chimeric antigen receptor [CAR] T-cell therapy). The significant impact the latter has had on patients' survival raises the all-important question of whether patients with t(11;14) should preferentially receive venetoclax-based treatments or T-cell engagers. While this would largely be dependent on access in many countries, sequencing remains a salient consideration. Evidence on the outcomes of t(11;14) patients treated with T-cell engagers is sparse, and future studies should report specifically on this when analyzing the impact of cytogenetics/FISH on treatment efficacy and patient survival. Certainly, the prospect of combining BCL2-inhibitors and a T-cell engager therapy is attractive, not just as targeted therapy in t(11;14) MM, but also due to its potential synergism. Venetoclax has been shown in pre-clinical studies to have immunomodulatory effects; in a study of samples from patients with chronic lymphocytic leukemia, flow cytometry analysis demonstrated less T-helper and T-cytotoxic T-cell exhaustion following venetoclax treatment.[69] This positive impact of BCL2-inhibitors on T-cell fitness can be harnessed to boost the efficacy of T-cell engagers, and raises interesting opportunities in terms of treatment sequencing. Potential regimens include utilizing BCL2-inhibitors as bridging therapy prior to CAR T-cell therapy or as maintenance treatment following CAR T-cell therapy. BCL2-inhibitors could also be used to limit exposure to bispecific/trispecific antibodies, and therefore minimize long-term side-effects. For example, one could consider a fixed duration of treatment with a bispecific/trispecific antibody followed by maintenance treatment with a BCL2-inhibitor, or even an alternating BCL2-inhibitor/T-cell engager therapy regimen to minimize T-cell exhaustion over time and reduce the risk of resistance. A clear area of unmet need is also in patients with concurrent t(11;14) and del(17p) and/or 1q+. Currently, the literature remains sparse in terms of the best BCL2-inhibitor-based treatment combination in this high-risk population. In this cohort, the concept of combining BCL2-inhibitors and T-cell engager therapy is an attractive one.

Certainly, for a BCL2-inhibitor/T-cell engager combination to be feasible, it is also vital to consider the overlapping and cumulative infection risk of these two agents. Studies should be designed with this in mind. Indeed, stringent anti-infective prophylactic strategies are crucial in any BCL2-inhibitor regimen and should be initiated from the start. These include prophylaxis against shingles (e.g., valaciclovir) for all patients, and against *Pneumocystis jirovecii* pneumonia (e.g., trimethoprim/sulfamethoxazole), especially in heavily pre-treated patients. Adequate use of filgrastim for the treatment and/or prophylaxis of neutropenia as well as early immunoglobulin replacement therapy for hypogammaglobulinemia are also strongly encouraged. Future studies should also consider incorporating response-adapted therapy. A MRD-adapted strategy in which patients with sustained MRD-negativity could cease therapy would certainly be beneficial to minimize toxicities, particularly the risk of infection that comes with prolonged exposure to BCL2-inhibitors as reported in the BELLINI study.[44]

While t(11;14) remains the main current biomarker for response to BCL2-inhibitor therapy, it is arguably an oversimplified method of patient selection. High BCL2/BCL-XL and BCL2/MCL1 ratios are certainly not exclusive to the t(11;14) cohort.[37] There is a need for more data on the efficacy of BCL2-inhibitors in patients without t(11;14) who have high expression of BCL2, who may indeed be missing out on an effective treatment option. This must start firstly with standardization of techniques of BCL2-protein quantification, including the determination of the optimal cut-off that defines high expression of BCL2 in relation to sensitivity to BCL2-inhibitor treatment. Considering the variability of BCL2-protein expression even within the t(11;14) cohort,[37] this may also help to stratify t(11;14) patients who have low BCL2 expression in whom BCL2-inhibition may not in fact be the optimal option, with preference for alternative treatment regimens instead.

Ongoing work is also required to better understand the diverse mechanisms of resistance to BCL2-inhibitors in myeloma cell lines. It is vital that rational BCL2-inhibitor-based treatment regimens take into consideration potential mechanisms of drug resistance (Figure 1D), and should include combination therapies, such as MCL1 and BCL-XL inhibitors, in order to empirically circumvent pathways that can promote escape from targeted BCL2-inhibition.

In order to further our understanding of how best to place BCL2-inhibitors in the current treatment landscape and also to pave the way for regulatory approval, future clinical trials of BCL2-inhibitors in t(11;14) MM should be carefully designed to ensure that they are sufficiently powered, with a clinically relevant control arm, vigilant consideration of overlapping toxicities when used in combination with other anti-myeloma drugs, and with clinically meaningful correlative studies incorporated at the outset. Given the 20% incidence of t(11;14) MM, large cooperative multicenter studies are preferred to facilitate robust and timely patient recruitment in a rapidly moving field.

Conclusion

Translocation t(11;14) is a key biomarker for predicting response to BCL2-inhibitors in MM, and its identification is becoming increasingly important with the advent of BCL2-targeted therapies. As a primary cytogenetic lesion, t(11;14) not only predicts sensitivity to BCL2-inhibition but also correlates with suboptimal responses to IMiD/PI-based induction therapy. This defines a population with an unmet clinical need, one that may benefit from the incorporation of BCL2-inhibitors early in the treatment course, rather than reserving these drugs for the relapsed/refractory setting. Further investigation is required to study the utility of BCL2-inhibition in upfront treatment of NDMM patients, examine BCL2-inhibitor combinations that can overcome additional high-risk chromosomal abnormalities that are present at either diagnosis or relapse, and explore the role and placement of BCL2-inhibitors in the era of T-cell engager therapies. While BCL2-inhibitors are yet to receive regulatory approval, they are the treatment of choice in t(11;14) MM.

Disclosures

BD has received honoraria from Bristol-Myers Squibb and Karyopharm; has provided consulting or advisory services for Bristol-Myers Squibb, Janssen, Arcellx, Kite Pharma, Pfizer, Karyopharm, Genentech, Natera and Sanofi and has participated in speakers' bureau for Janssen, Sanofi, Karyopharm and Bristol-Myers Squibb. HQ has received grants or contracts from AbbVie, Bristol-Myers Squibb, Antengene, GlaxoSmithKline, Karyopharm and Sanofi and has had a leadership or fiduciary role in advisory boards for AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Pfizer, Antengene and Sanofi. SS has no conflicts of interest to disclose.

Contributions

All authors contributed critically to the contents of this manuscript.

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