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Review Article

Multiple myeloma with t(11;14): unique biology and evolving landscape

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Abstract: Multiple myeloma is characterized by heterogeneity in clinical presentation, response to treatment, and importantly, patient outcomes. The translocation of chromosomes 11 and 14 [t(11;14)(q13;32)], hereafter referred to as t(11;14), is the most common primary translocation event in multiple myeloma, occurring in approximately 16%-24% of patients. Multiple myeloma harboring t(11;14) represents a unique disease subset as t(11;14)-positive myeloma cells exhibit biological features that are distinct from t(11;14)-negative myeloma cells, including overexpression of cyclin D1, higher levels of the antiapoptotic protein BCL-2, and the frequent expression of the B-cell lineage protein CD20. Additionally, t(11;14) is associated with less common clinical features, such as immunoglobulin M and light chain disease. With the evolution of the treatment landscape, the prognostic significance of t(11;14) multiple myeloma remains debatable. However, it is clear that t(11;14) multiple myeloma represents a distinct subset and a rare opportunity for targeted therapy with BCL-2 inhibition. In this review, we first describe the underlying biology of t(11;14) multiple myeloma cells, then summarize the body of literature evaluating the prognosis of patients with t(11;14) multiple myeloma, and finally discuss therapeutic implications.

Keywords: Multiple myeloma, t(11;14), prognosis, BCL-2, targeted therapy

Introduction

Multiple myeloma (MM) is a plasma cell neoplasia characterized by clonal proliferation of malignant plasma cells that acquire certain genetic changes during B-cell development and maturation. Structural and numeric chromosomal abnormalities, including translocations, occur mostly at disease onset. Over the course of disease progression or relapse, gene mutations contribute to the clonal heterogeneity and complexity of MM [1, 2]. These genetic abnormalities are important prognostic factors as they determine clinical presentation, response to therapy, and disease course [3, 4]. Due to the highly variable nature of MM, there is increasing focus on adopting precision medicine to tailor treatment to a patient's genetic subtype. The translocation of chromosomes 11 and 14 [i.e., t(11;14)(q13;q32)], hereafter referred to as t(11;14), is a primary cytogenetic abnormality found in approximately 16%-24% of patients with MM [5-15], making it the most common translocation [1, 4]. Additionally, this translocation has gained recognition as a predictive biomarker that can be targeted with BCL-2 inhibitors, such as venetoclax [16]. Thus, understanding the underlying biology of t(11;14) MM, the impact of this translocation on prognosis, and the response of t(11;14) MM to treatment are of particular importance. In this review, we describe the unique biology of MM cells harboring t(11;14), summarize the literature addressing the prognostic impact of this translocation, and discuss therapeutic implications for patients with t(11;14) MM.

t(11;14) is a unique subset of MM

Development of t(11;14) MM

MM is preceded by monoclonal gammopathy of undetermined significance (MGUS) [17, 18], which is a premalignant, asymptomatic condition characterized by the presence of clonal plasma cells in the bone marrow (BM). Normal plasma cells are derived from B cells, which initially develop in the BM but migrate into the peripheral blood and secondary lymphoid tissues for further development [19]. Upon antigen engagement in the periphery, mature B cells seed germinal centers and differentiate into memory and plasma cells; although terminally differentiated plasma cells exist in lymphoid organs, the majority of long-lived plasma cells home to the BM [20]. Primary cytogenetic abnormalities, such as immunoglobulin heavy chain gene (*IGH*) translocations or trisomies, acquired during B-cell development and maturation lead to the transformation of normal plasma cells into premalignant, clonal plasma cells. Proliferation of these cells within the BM results in MGUS, which can evolve into asymptomatic smoldering MM and ultimately symptomatic MM [17-19]. As a primary abnormality, t(11;14) is found in both MGUS and MM and can be detected by fluorescence in situ hybridization (FISH) or conventional metaphase cytogenetics, although the latter is used less frequently and often misses the abnormality given the low proliferation rate of plasma cells.

The t(11;14) translocation is found in approximately 50% of patients with AL amyloidosis, another clonal plasma cell dyscrasia closely related to MM [21, 22]. Additionally, t(11;14) is considered a hallmark feature of mantle cell lymphoma (MCL) [23], but molecular analyses have shown differences in the breakpoints found in MCL versus MM. In MCL, t(11;14) predominantly arises during B-cell development as an error of variable, diversity, and joining [V(D)J] recombination [24], and breakpoints tend to be clustered in a region known as the major translocation cluster or located at or near activation-induced cytidine deaminase hotspots [24-28]. In contrast, translocations in MM, including t(11;14), are thought to occur in mature B cells undergoing class switch recombination in germinal centers [29-31], and analyses have shown t(11;14) breakpoints scattered throughout the 11q13 region, with none found within the MCL major translocation cluster [26, 28, 31-35]. However, several more recent molecular analyses have identified V(D)J recombination-induced breakpoints in t(11;14) MM [31, 36], indicating that in some cases, t(11;14) myeloma clones may originate from pre-germinal-center B cells. As the most commonly detected translocation, a deeper understanding of t(11;14) MM disease biology is warranted.

Biology of t(11;14) MM

The t(11;14) translocation involves *IGH* on chromosome 14 and the proto-oncogene *CCND1* on chromosome 11, resulting in the overexpression of cyclin D1 [36-39]. MM cells harboring t(11;14) exhibit distinct cellular features, such as lymphoplasmacytic morphology [38, 40-43], which are not associated with other abnormalities. In addition, some t(11;14) MM shows a unique dependence on the anti-apoptotic protein BCL-2 (encoded by *BCL2*). Both normal plasma cells and most MM cells without t(11;14) primarily depend on the anti-apoptotic protein MCL-1 (encoded by *MCL1*) for survival [44-48], although some MM cells are codependent on MCL-1 and BCL-X_L (encoded by *BCL2L1*) or BCL-2 [49]. In contrast, elevated levels of BCL-2 and high *BCL2/MCL1* and *BCL2/BCL2L1* ratios have been associated with t(11;14) MM cells [36, 39, 50, 51], indicating BCL-2 is important for their survival. However, high BCL-2 expression is not exclusive to t(11;14) MM and has been observed in other subtypes [39, 51, 52].

In addition to having distinct oncogenic features, there is increasing evidence that t(11;14) MM cells often lack traditional plasma cell markers that are detected on other MM cell types and exhibit remnants of B-cell biology. Expression of the B-cell lineage membrane protein CD20 and higher levels of the B-cell receptor component CD79a have been detected in t(11;14) MM cells [8, 36, 38, 40, 43, 53, 54]. Additionally, t(11;14) MM cells have demonstrated decreased expression of the plasma cell marker CD38, which inversely correlated with the *BCL2/BCL2L1* ratio [43], and decreased expression of the adhesion molecule CD56 [8, 36, 53-55], which might be involved in the ability of MM cells to migrate from the

BM [56]. Several studies have detected overexpression of B-cell-associated genes in t(11;14) MM cells, including *PAX5* [12, 43], a transcription factor that must be silenced for the terminal differentiation of B cells to plasma cells. This B-cell-associated gene expression has been shown to be associated with sensitivity to the oral BCL-2 inhibitor venetoclax [57]. However, among patients with *CCND1*-activating lesions, gene expression profiling has identified 2 distinct groups, with the expression of more than 100 genes, including *PAX5* and the gene encoding CD20, significantly differing between these groups [12]. These results indicate there may be distinct subgroups among patients with t(11;14), which has been further supported by several studies that have observed differences in CD20 surface expression on MM cells with t(11;14) or *CCND1* overexpression [8, 53, 58]. Overall, t(11;14) MM is distinguished as a special subset of MM due to the unique biology of MM cells harboring this translocation, and these features are important factors to consider when making treatment decisions for patients with t(11;14) MM.

Clinical presentation of t(11;14) MM

Several common clinical features have been noted among patients with t(11;14), such as higher rate of bone disease [38, 59, 60]; higher incidences of immunoglobulin M, immunoglobulin D, light chain, and non-secretory disease [6, 8, 36, 42, 59, 61-66]; and higher rate of renal dysfunction due to cast nephropathy [64]. Studies show it is common for a patient with t(11;14) to have a coexisting abnormality [8, 59, 62, 64-68], with several of these studies observing chromosome 13 abnormalities in >30% of patients with t(11;14) [8, 59, 68]. Finally, t(11;14) is prevalent in primary plasma cell leukemia (approximately 33%-71%) [6, 8, 69, 70], an aggressive variant of MM associated with very poor prognosis. Together, these clinical features further distinguish t(11;14) as a unique subset of MM.

Impact of t(11;14) by race

Recently published findings from 2 observational studies indicate differing outcomes with t(11;14) MM between patients of different races [14, 64]. While no difference was observed in progression-free survival (PFS), both studies reported prolonged overall survival in African American patients with t(11;14) MM compared with non-African American or White patients with t(11;14) MM [14, 64]. One of these studies found a higher likelihood of death and an increased risk of early mortality in African American patients with t(11;14) compared with those without t(11;14) [14]. Overall, these results indicate that there may be complex interplay between race and t(11;14) MM disease biology; further studies are needed to clarify the impact of this translocation on the survival of African American patients.

Prognosis of t(11;14) MM

The pre-novel agent era

Initial studies evaluating the outcomes of t(11;14) MM were small. Additionally, most of these studies assessed the translocation using conventional cytogenetics, and several analyses combined patients with any 11q abnormality [63, 71-73]. Collectively, these initial studies alluded to a possible negative impact due to the presence of t(11;14). However, as FISH testing became available in the 1990s, additional studies were published, and larger retrospective studies indicated patients with t(11;14) have similar, if not more favorable, outcomes compared with patients without t(11;14) (**Table 1**) [74-76]. These findings were corroborated by analyses of prospective clinical trial cohorts, and the aggregate results confirmed that patients with t(11;14) had similar or favorable outcomes compared with other patient groups (**Table 1**) [5, 7, 13, 77].

At the end of the pre-novel era, the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines were developed to guide treatment of newly diagnosed MM [78]. While the International Staging System determines patient risk by laboratory parameters [79], the mSMART guidelines favor a cytogenetic and proliferation-based model to predict risk stratification [78]. Based on the collective data published during the pre-novel era [7, 61, 72, 73, 76, 80, 81], the mSMART guidelines classified t(11;14) MM as a standard-risk abnormality [78, 82]. Thus, the presence of t(11;14) did not negatively impact outcomes at the end of the pre-novel agent era.

The novel agent era

In the early to mid 2000s, novel targeted agents, such as the immunomodulatory drug

Table 1. Outcomes for patients with t(11;14) multiple myeloma

Publication	Study Details	Follow-Up Time	Cytogenetic Subgroups	Outcomes
Fonseca et al. *Blood* 2002 [5]	Study type: Clinical trial E9486 and correlative laboratory study E9487 Patient population: NDMM, N=351 Treatment: VBMCP vs VBMCP + interferon-α2 vs VBMCP + high-dose cyclophosphamide t(11;14) detection method: FISH Additional details: Patients were required to have prolonged follow-up information and known clinical outcomes	108 mo for survivors included in the E9486 trial	t(11;14), n=53 Non-t(11;14), n=283	t(11;14) vs. non-t(11;14) PFS: 33 mo vs. 27.1 mo (*P*>0.2) OS: 49.6 mo vs. 38.7 mo (*P*>0.2)
Moreau et al. *Blood* 2002 [74]	Study type: Retrospective Study period: Jan 1995 to Dec 2000 Study centers: The University Hospital in Nantes or Lille, France Patient population: NDMM, N=168 Treatment: Intensive therapies, including 4-5 courses of VAD followed by ≥1 course of high-dose therapy t(11;14) detection method: FISH	27 mo for surviving patients	t(11;14), n=26 t(4;14), n=22 Others,[a] n=120	t(11;14) vs. t(4;14) vs. others OS at 80 mo: 87.5% vs. 22.8% vs. 60%
Dewald et al. *Blood* 2005 [75]	Study type: Retrospective Study period: March 1989 to Oct 2002 Study center: Mayo Clinic Patient population: NDMM, N=154 t(11;14) detection method: FISH Additional details: Patients were required to have BM specimens collected within 30 days of diagnosis	26.2 mo	Metaphase FISH: t(11;14) without t(4;14), t(14;16), 17p-, or 13q-, n=6 t(4;14), t(14;16), 17p-, or 13q-, n=33 Normal, n=93 Interphase FISH: t(11;14) without t(4;14), t(14;16), 17p-, or 13q-, n=15 t(4;14), t(14;16), n=20 13q- or 17p- without t(4;14), t(14;16), n=59 Normal, n=21	Metaphase FISH t(11;14) vs. t(4;14), t(14;16), 17p-, or 13q- vs. normal OS: 31.0 mo vs. 13.9 mo vs. 46.7 mo Interphase FISH t(11;14) vs. t(4;14), t(14;16) vs. 13q- or 17p- vs. normal OS: 55.3 mo vs. 13.3 mo vs. 33.9 mo vs. 45.0 mo
Gertz et al. *Blood* 2005 [76]	Study type: Retrospective Study period: Jan 1990 to Sept 2001 Study center: Mayo Clinic Patient population: MM, N=238 Treatment: ASCT t(11;14) detection method: FISH Additional details: Patients were required to have pre-transplantation FISH on BM aspirates	36 mo minimal follow-up for surviving patients	t(11;14), n=34 Non-t(11;14), n=163	t(11;14) vs. non-t(11;14) PFS: 20.1 mo vs. 15.3 mo OS: 36.6 mo vs. 34.8 mo
Avet-Loiseau et al. *Blood* 2007 [7]	Study type: Clinical trials IFM99-02, IFM99-03, and IFM99-04 Patient population: NDMM, N=1064 Treatment: VAD with tandem ASCT (IFM99-02 and IFM99-04) and VAD with ASCT then reduced-intensity alloSCT (IFM99-03) t(11;14) detection method: FISH	41 mo for surviving patients	t(11;14), n=154 Non-t(11;14), n=592	t(11;14) vs. non-t(11;14) EFS: 35 mo vs. 34 mo (*P*=0.2) OS at 41 mo: 80% vs. 74% (*P*=0.28)

Gutiérrez et al. *Leukemia* 2007 [77]	Study type: Clinical trial GEM-2000 Patient population: NDMM, N=260 Treatment: VBMCP/VBAD induction followed by ASCT t(11;14) detection method: FISH Additional details: Patients were required to have BM plasma cell infiltration above 10% by flow cytometry	34 mo for surviving patients	t(11;14), n=34 Non-t(11;14), n=226	t(11;14) vs. non-t(11;14) OS: 49 mo vs. 40 mo (*P*-value NS)
An et al. *Leuk Res* 2013 [8]	Study type: Retrospective Study period: Jan 2004 to Dec 2012 Patient population: Plasma cell dyscrasia, N=350 (NDMM, n=253; RRMM, n=77; pPCL, n=10; sPCL, n=10) Treatment: Thalidomide- or bortezomib-based regimen t(11;14) detection method: FISH	3 y	Thalidomide-based t(11;14)[b] Non-t(11;14) Bortezomib-based t(11;14)[b] t(11;14) CD20- t(11;14) CD20+ Non-t(11;14)	Thalidomide-based t(11;14) vs. non-t(11;14) PFS: 23.0 mo vs. 18.0 (*P*=0.819) OS: 30.0 mo vs. 21.0 mo (*P*=0.902) Bortezomib-based t(11;14) vs. non-t(11;14) PFS: 28.7 mo vs. 32.5 mo (*P*=0.745) OS: 54.0 mo vs. 36.0 mo (*P*=0.612) Bortezomib-based t(11;14) CD20- vs. t(11;14) CD20+ PFS: 11.0 mo vs. 43.0 mo (*P*=0.005) OS: 16.5 mo vs. 54.0 mo (*P*=0.016)
Sasaki et al. *Biol Blood Marrow Transplant* 2013 [85]	Study type: Retrospective Study period: Feb 2000 to Aug 2010 Study center: MD Anderson Cancer Center Patient population: Symptomatic MM, N=993 Treatment: ASCT t(11;14) detection method: CC or FISH Additional details: Patients were required to have cytogenetic results before ASCT	37 mo in surviving patients	t(11;14), n=27 HR,[c] n=97 Normal, n=869	t(11;14) vs. HR PFS: 23 mo vs. 9.7 mo 3-y PFS: 27% vs. 13% (*P*=0.05) OS: 51 mo vs. 21 mo 3-y OS: 63% vs. 34% (*P*=0.04) t(11;14) vs. normal PFS: 23 mo vs. 33 mo 3-y PFS: 27% vs. 47% (*P*=0.02) OS: 51 mo vs. 87 mo 3-y OS: 63% vs. 82% (*P*=0.01)
Pawlyn et al. *Blood* 2015 [13]	Study type: Clinical trial MRC Myeloma IX (enrollment between 2003 and 2007) Patient population: Symptomatic NDMM, N=847 Treatment: Intensive regimens (CVAD vs. CTD) or non-intensive regimens (MP vs. CTDa) t(11;14) detection method: FISH Additional details: Patients were required to have a complete, valid data set for all adverse cytogenetic lesions and hyperdiploidy	NA for population used for cytogenetic analysis	t(11;14), n=127 Non-t(11;14), n=720	t(11;14) vs. non-t(11;14) PFS: 21.3 mo vs. 17.1 mo (*P*-value NS) OS: 51.1 mo vs. 45.8 mo (*P*-value NS)
Shin et al. *Clin Lymphoma Myeloma Leuk* 2015 [87]	Study type: Retrospective Study period: April 2004 to Dec 2012 Study centers: 3 unnamed centers in Korea Patient population: MM with extramedullary plasmacytoma, N=58 Treatment: ASCT t(11;14) detection method: FISH Additional details: Patients included in the study had available FISH results for 1 or more chromosomal abnormality in BM samples obtained at diagnosis	35 mo for surviving patients	t(11;14), n=7 Non-t(11;14), n=40	t(11;14) vs. non-t(11;14) PFS: 12 mo vs. 27 mo (hazard ratio, 25.154; *P*<0.001) OS: 16 mo vs. NR (hazard ratio, 7.484; *P*=0.024)

Kaufman G et al. *Leukemia* 2016 [10]	Study type: Retrospective Study period: 2003 to 2012 Study center: Mayo Clinic Patient population: NDMM, N=409 Treatment: ASCT within 12 mo of diagnosis t(11;14) detection method: FISH Additional details: Patients included in the study had evaluable FISH within 6 mo of diagnosis	43.0 mo	t(11;14), n=69 SR, n=244 HR,[d] n=96	t(11;14) vs. SR vs HR PFS: 28.1 mo vs. 30.4 mo vs. 24.9 mo (*P*=0.034) OS: 73.4 mo vs. 103 mo vs. 60.5 mo (*P*<0.0001)
Kaufman J et al. *Blood* 2018 [86]	Study type: Retrospective Study period: July 2005 to Aug 2016 Study center: Winship Cancer Institute Patient population: NDMM, N=867 Treatment: RVD induction t(11;14) detection method: FISH Additional details: Patients were required to have FISH results for t(11;14)	39 mo for PFS 38 mo for OS	t(11;14), n=122 SR,[e] n=527	t(11;14) vs. SR non-t(11;14) PFS: 51 mo vs. 75 mo (*P*<0.001) OS: NR vs. NR
Lakshman et al. *Leukemia* 2018 [59]	Study type: Retrospective Study period: Jan 2004 to Nov 2014 Study center: Mayo Clinic Patient population: MM, N=1095 t(11;14) detection method: FISH Additional details: Patients were required to have cytogenetic results; 2 patients with MM with normal or any non-t(11;14) abnormality and matching age and year of diagnosis were identified for each patient with t(11;14) MM	66.2 mo	t(11;14), n=365 Non-(11;14) translocation,[f] n=132 No translocation, n=598	t(11;14) vs. non-(11;14) translocation PFS: 23.0 mo vs. 19.0 mo (*P*=0.01) OS: 74.4 mo vs. 49.8 mo (*P*<0.001) 5-y OS: 57.8% vs. 41.7% t(11;14) vs. no translocation PFS: 23.0 mo vs. 28.3 mo (*P*=0.01) OS: 74.4 mo vs. 103.6 mo (*P*=0.003) 5-y OS: 57.8% vs. 68.1%
Saini et al. *Clin Cancer Res* 2019 [67]	Study type: Retrospective Study period: Jan 2006 to Dec 2015 Study center: MD Anderson Cancer Center Patient population: Symptomatic MM, N=160 Treatment: ASCT t(11;14) detection method: FISH Additional details: Patients were required to have data available for CC or FISH, and patients with t(11;14) detected by CC only were excluded; matched pairs for t(11;14) and SR were created via a 1:1 propensity-score matched control without replacement	42.7 mo for the overall matched cohort (N=160)	t(11;14), n=80 SR, n=80	t(11;14) vs. SR PFS: 29.9 mo vs. 51.9 mo (*P*=0.14) 4-y PFS: 40.8% vs. 51.1% OS: NR vs. NR (*P*=0.17) 4-y OS: 74.9% vs. 88.3%
Miura et al. *Blood 2019* [53]	Study type: Retrospective Study period: April 2009 to July 2019 Study center: Kameda Medical Center Patient population: NDMM, N=234 t(11;14) detection method: FISH Additional details: Patients included in the study had cytogenetic analysis data available	NA	t(11;14), n=57 No specific abnormality,[g] n=137 t(4;14) or t(14;16), n=29	t(11;14) vs. no specific abnormality: PFS: 34.2 mo vs. 55.6 mo (*P*=0.036) OS: 51.2 mo vs. NR (*P*=0.11) t(11;14) vs. t(4;14) or t(14;16) PFS: 34.2 mo vs. 30.2 OS: 51.2 mo vs. 79.8 mo

Gran et al. *Eur J Haematol* 2019 [88]	Study type: Retrospective Study period: May 2005 to Sep 2018 Study center: Karolinska University Hospital Patient population: NDMM, N=469 t(11;14) detection method: FISH Additional details: Patients included in the study were evaluated at time of diagnosis for t(11;14)	40.3 mo	t(11;14) SR,[h] n=63 t(11;14) HR,[h] n=26 Non-t(11;14) SR,[h] n=204 Non-t(11;14) HR,[h] n=176	t(11;14) SR vs. non-t(11;14) SR PFS: 28.9 mo vs. 35.5 mo (P=0.22) 5-y PFS[i]: 29.2% vs. 23.6% (P=0.2) 5-y OS: 65.5% vs. 73.9% (P=0.4) t(11;14) HR vs. non-t(11;14) SR PFS: 24.1 mo vs. 35.5 mo 5-y PFS[i]: 13.2% vs. 23.6% (P=0.01) 5-y OS: 42.5% vs. 73.9% (P=0.1) t(11;14) HR vs. non-t(11;14) HR PFS: 24.1 mo vs. 27.2 mo (P=0.22) 5-y PFS[i]: 13.2% vs. 18.7% 5-y OS: 42.5% vs. 54.1%
Gao et al. *Front Oncol* 2020 [62]	Study type: Retrospective Study period: March 2003 to Jan 2018 Study centers: Beijing Chaoyang Hospital, Shanghai Changzheng Hospital, and Guangzhou Zhongshan Hospital Patient population: Symptomatic NDMM, N=455 Treatment: ≥1 ASCT within 12 mo of treatment initiation t(11;14) detection method: FISH Additional details: Patients were required to have FISH results prior to treatment initiation	35.8 mo	t(11;14), n=55 SR,[j] n=248 HR,[j] n=152	t(11;14) vs. SR PFS: 52 mo vs. 63 mo (P=0.935) OS: 86 mo vs. 100 mo (P=0.836) t(11;14) vs. HR PFS: 52 mo vs. 33 mo (P=0.009) OS: 86 mo vs. 71 mo (P=0.041)
Bal et al. *Br J Haematol* 2021 [65]	Study type: Retrospective Study period: Jan 2011 to Feb 2020 Data source: Flatiron database Patient population: MM, N=5581 t(11;14) detection method: FISH Additional details: Patients included in the study had FISH results within 90 days of diagnosis	37 mo for PFS 35 mo for OS	t(11;14) with no HR abnormality, n=589 Non-t(11;14) with no HR abnormality, n=2909	t(11;14) vs. non-t(11;14) PFS: 36.1 mo vs. 40.1 mo (hazard ratio, 1.16; P=0.028) OS: 72 mo vs. 77 mo (hazard ratio, 1.12; P=0.19)
Gasparetto et al. *Clin Lymphoma Myeloma Leuk* 2022 [14]	Study type: Prospective observational cohort study Data source: Connect MM Registry Patient population: NDMM, N=1574 t(11;14) detection method: CC or FISH Additional details: Only patients who were tested for t(11;14) were included in the analysis	NA for population used for t(11;14) analysis	t(11;14), n=378 Non-t(11;14), n=1196	t(11;14) vs. non-t(11;14) PFS: 34.8 mo vs. 35.7 mo (hazard ratio, 1.02; P=0.7675[k]) OS: 74.0 mo vs. 77.3 mo (hazard ratio, 0.99; P=0.9417[k])

[a]Patients with either no 14q32 rearrangements, rearrangements with another unknown chromosomal partner, or t(14;16) [74]. [b]t(11;14) was detected in 60 patients with NDMM, 14 with RRMM, 6 with pPCL, and 5 with sPCL. t(11;14) thalidomide- and bortezomib-based treatment subgroup n values NA [8]. [c]HR included del(13q)/-13 or hypoploidy by CC, or t(4;14), t(14;16), t(14;20) or del(17p13) by CC or FISH [85]. [d]HR included del(17p), t(4;14), t(14;16), or t(14;20) by FISH [10]. [e]Patients carrying del(17p), t(4;14), t(14;16), and a complex karyotype based on metaphase cytogenetics were excluded [86]. [f]Included patients with a defined non-(11;14) translocation, such as t(4;14), t(6;14) or t(14;20) [59]. [g]Patients did not have t(11;14), t(4;14), t(14;16), or del(17p) [53]. [h]Patients were grouped as HR or SR based on the International Myeloma Working Group consensus criteria [88, 104]. [i]Based on available data: t(11;14) HR, n=25; t(11;14) SR, n=53; non-t(11;14) HR, n=155; non-t(11;14) SR, n=178 [88]. [j]SR included patients without t(11;14), t(4;14), t(14;16), and del(17p); HR included patients with t(4;14), t(14;16), and/or del(17p) [62]. [k]P-value adjusted for patient cohort, age group, medical history of solitary plasmacytoma, surgery for myeloma, del(17p), t(14;16), t(4;14), and platelet count [14]. alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; BM, bone marrow; CC, conventional cytogenetics; CTD, cyclophosphamide, thalidomide, and dexamethasone; CTDa, cyclophosphamide, thalidomide, and dexamethasone with attenuated dosing; CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; EFS, event-free survival; FISH, fluorescence in situ hybridization; HR, high risk; MM, multiple myeloma; MP, melphalan and prednisolone; NA, not available; NDMM, newly diagnosed multiple myeloma; NR, not reached; NS, not significant; OS, overall survival; PFS, progression-free survival; pPCL, primary plasma cell leukemia; RRMM, relapsed/refractory MM; RVD, lenalidomide, bortezomib, and dexamethasone; sPCL, secondary plasma cell leukemia; SR, standard risk; VAD, vincristine, doxorubicin, and dexamethasone; VBAD, vincristine, carmustine, doxorubicin, and dexamethasone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, and prednisone.

thalidomide and the proteasome inhibitor bortezomib, were approved for the treatment of relapsed/refractory MM (RRMM) and eventually newly diagnosed MM. Overall, the uptake of novel agents has translated into improved overall survival for patients with MM [83, 84]. Yet, studies in the novel agent era have shown varying results regarding outcomes for patients with t(11;14) compared with patients with standard- or high-risk cytogenetics (**Table 1**).

The largest cohort of patients with MM carrying t(11;14) revealed significantly shorter PFS for patients with t(11;14) with no high-risk abnormality compared with patients without t(11;14) with no high-risk abnormality (**Table 1**), even after adjustment for covariables [65]. In contrast, a more recent analysis published in 2022 identified the second largest cohort of patients with t(11;14) MM and found no differences in outcomes between patients with and without t(11;14) (**Table 1**) [14]. However, comparing the results of studies evaluating the prognosis of t(11;14) MM in the era of novel agents is challenging due to differences in methodology, patient populations, and treatments used, making it difficult to draw firm conclusions on the impact of t(11;14) (**Table 1**) [10, 59, 62, 67, 85, 86]. Importantly, the treatments used when t(11;14) was first tested as a prognostic biomarker versus current studies are vastly different.

Some studies have identified subsets of patients with t(11;14) who may have poorer outcomes. Two analyses have observed inferior outcomes for patients with t(11;14) lacking CD20 compared with those displaying CD20 (**Table 1**) [8, 53]. Poor outcomes have also been observed for patients with t(11;14) MM who had extramedullary plasmacytoma (**Table 1**) [87] and when autologous stem cell transplantation (ASCT) was not performed [88]. In some instances, t(11;14) is associated with very aggressive MM, such as in primary plasma cell leukemia where this translocation is found in approximately 33%-71% of patients [6, 8, 69, 70]. Together, these studies suggest a differential impact of t(11;14) on prognosis based on additional disease characteristics or the type of treatment received.

While the treatment landscape has evolved, some studies have produced conflicting results regarding the prognostic impact of t(11;14) MM. Both the revised International Staging System and the updated mSMART consensus guidelines continue to consider patients with t(11;14) as an isolated abnormality as standard risk [89, 90]. However, the concomitant presence of secondary cytogenetic abnormalities, like del(17p), may influence outcomes for patients with t(11;14) [65-68]. Nonetheless, the opportunity to develop targeted therapies for t(11;14) MM, and the use of such therapies, remains independent of prognostic relevance.

Therapeutic implications of t(11;14) MM

The introduction of novel agents has improved outcomes for patients with MM; however, some studies suggest treatment with proteasome inhibitors may result in limited benefit for patients with t(11;14) MM or AL amyloidosis [65, 86, 91]. Some studies have suggested that treatment with intensive therapies or ASCT results in favorable outcomes for patients with t(11;14) [7, 67, 74, 76, 77, 88].

Improved understanding of t(11;14) MM may enable the development of new treatment strategies based on the distinctive biology of these malignant plasma cells. The novel agent venetoclax may be uniquely positioned for the treatment of t(11;14) MM. Venetoclax is a highly selective, potent, oral BCL-2 inhibitor and represents the first targeted therapy for MM, as t(11;14) cells seem to have higher ratios of BCL-2 to MCL-1, rendering these myeloma cells particularly susceptible to BCL-2 inhibition [50, 51, 57, 92]. Various combinations of venetoclax are under investigation, with the goal of enhancing venetoclax activity through complementary mechanisms, such as increasing BCL-2 dependency in MM cells with dexamethasone [93]. In clinical trials, venetoclax has demonstrated efficacy in patients with t(11;14) MM when given as monotherapy [51, 94], and enhanced efficacy was observed when venetoclax was given as combination therapy [52, 95-98].

Several ongoing clinical trials are further evaluating the safety and efficacy of these investigational venetoclax combinations for the treatment of RRMM. CANOVA is a phase 3 study (NCT03539744) evaluating the combination of venetoclax and dexamethasone versus pomalidomide and dexamethasone for the treatment of t(11;14) RRMM. While the effi-

cacy and safety of bortezomib added to venetoclax combined with dexamethasone have already been demonstrated [52, 95], the open-label, phase 2, dose-escalation M15-538 study (NCT02899052) is evaluating carfilzomib as the proteasome inhibitor added to venetoclax plus dexamethasone for the treatment of t(11;14) RRMM.

While most MM cells have robust surface expression of CD38, a recent study showed significantly decreased CD38 expression in patients with t(11;14) MM [43]. However, decreased CD38 expression is also observed in patients who have sustained and deep response to daratumumab [99, 100], indicating this reduction is not necessarily an escape mechanism. Furthermore, MM cells with decreased CD38 expression may have impaired adhesion to stromal cells via CD38-CD31 interactions, resulting in reduced growth and decreased protection against apoptosis [101, 102]. Antibody-dependent cellular phagocytosis induced by daratumumab has been enhanced by venetoclax in a preclinical model of double-hit lymphoma [103], providing the rationale for combining these agents. Venetoclax, daratumumab, and dexamethasone are being studied with or without bortezomib in patients with RRMM in the 3-part, phase 1/2 M15-654 study (NCT03314181). Initial results indicate deep and durable responses [96], suggesting that the combination may be synergistic and provide further benefit.

MM harboring t(11;14) clearly establishes itself as a special subset of MM with its unique biology, such as B-cell-associated gene and protein expression, and association with less common clinical features, including immunoglobulin M and light chain disease. Moreover, the growing evidence indicating t(11;14) may occur during an earlier stage of B-cell development further separates t(11;14) MM from other subtypes. Ultimately, these unique features combined with the opportunity to effectively treat t(11;14) MM with therapies that target the biology of these malignant cells warrant the recognition of t(11;14) MM as a separate entity in the coming years.

Over time, treatment of MM may evolve toward precision medicine, in which cytogenetic abnormalities are assessed and considered for therapeutic decision making in earlier lines of therapy. Accordingly, the MyDRUG study (NCT03732703) is an ongoing phase 1/2 study evaluating the use of precision medicine to treat patients with RRMM who received at least 1 but no more than 3 prior therapies. In this study, patients are assigned to a treatment arm based on the presence of certain mutations or t(11;14); patients with t(11;14) MM will receive venetoclax in combination with ixazomib, pomalidomide, and dexamethasone.

In conclusion, the prognostic significance of t(11;14) MM remains debatable, as studies continue to show varying outcomes for patients harboring t(11;14) and may evolve with the changing treatment landscape. Irrespective of its prognosis, t(11;14) MM clearly exhibits unique biology and response to therapies, with targeted therapies, such as venetoclax, showing promising efficacy. A deeper understanding of the distinct disease biology of t(11;14) MM and the potential availability of a targeted therapy may allow for improved outcomes for patients with t(11;14) MM. To this end, routine FISH testing should be performed at the time of diagnosis and relapse, and future clinical trials should evaluate the incorporation of these therapies into earlier lines of treatment. Given that t(11;14) is indicative of a different biology, rather than a risk group, testing for this translocation is of utmost importance to ensure that patients carrying t(11;14) receive the most appropriate treatment available.

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