Translocation (14;16) Positive Multiple Myeloma: Clinical Features and Survival Outcomes of a High-risk Population

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Abstract

CONTEXT: Multiple myeloma (MM) is characterized by recurrent chromosomal abnormalities (CA), which are known to affect patient survival. Translocation t(14;16) is associated with inferior survival, but the clinical features and outcomes of these patients have not been thoroughly described.

OBJECTIVE: To characterize the baseline characteristics, response to first-line treatment, and survival outcomes of patients with t(14;16) multiple myeloma.

DESIGN: We retrospectively reviewed databases of patients treated for multiple myeloma at participating medical centers in the United States, Italy, and Greece. Patients carrying t(14;16) as detected by FISH diagnosed between December 2006 and March 2017 were included.

RESULTS: A total of 123 patients were evaluated. Median age at diagnosis was 66 years; 49% of patients presented with hemoglobin ≤ 10 g/dl and 11% with platelets $\leq 100 \times 10^9/L$. Elevated lactate dehydrogenase (LDH), hypercalcemia and creatinine values >2 mg/dl were observed in 19%, 17% and 13%, respectively and 43% had ISS and R-ISS stage 3 disease. Eighty-two percent had at least one additional unfavorable CA, including del13q (71%), del17p (22%) and 1q gain (27%). Induction therapy consisted of an immunomodulatory drug, a proteasome inhibitor or a combination of both in 43%, 29% and 28%, respectively. Consolidation with autologous transplantation in first remission (ASCT-1) was performed in one-fourth of patients, and 43% received maintenance therapy. The best response to first-line treatment was $\geq$ partial response (PR) in 83%, with 26% $\geq$ complete remission (CR). Median progression-free survival (PFS) and overall survival (OS) for the entire cohort were 19 and 53 months, respectively. Among ASCT-eligible patients, those who received ASCT-1 had longer median PFS (31 vs. 10 months; HR: 0.35, $p=0.003$) and OS (58 vs. 34 months; HR 0.48, $p=0.04$) compared to those who did not. In ASCT-ineligible patients, median PFS and OS were 16 and 59 months. Maintenance therapy significantly prolonged median PFS (36 vs. 19 months, HR:0.56; $p=0.03$) compared to no maintenance.

CONCLUSIONS: In the largest cohort of t(14;16) patients described to date, t(14;16) characterizes a group of high-risk MM patients with poor PFS and OS. ASCT-1 in first remission prolonged survival and maintenance therapy improved progression-free survival of patients with t(14;16).

Background

- The implementation of novel triplet-based induction regimens, consolidation with autologous stem cell transplant, and maintenance therapy has helped to improve outcomes significantly for patients with multiple myeloma, with median PFS ranging from 35 to 50 months [1,2] and overall survival rates reported as high as 75 months. [3]
- However, for many patients with high-risk features and cytogenetics, outcomes remain poor.
- Translocation (14;16) has been implicated as a high-risk recurrent cytogenetic abnormality seen in multiple myeloma, resulting in inferior outcomes including survival [4-6]. However, as it is a relatively infrequent event, occurring in approximately 5% of newly-diagnosed patients [4], the clinical features and outcomes of t(14;16) myeloma have not been fully described, particularly in the era of novel therapies.
- The primary objective of this analysis was to describe the clinical characteristics, response to first-line therapy and survival outcomes of newly-diagnosed multiple myeloma patients (NDMM) harboring t(14;16) by FISH.

References

- Einsele, H., et al., Phase II study of bortezomib, cyclophosphamide and dexamethasone as induction therapy in multiple myeloma: DSMM XI trial. Br J Haematol, 2017. 179(4): p. 586-597.
- Aitai, M., et al., Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017; 376(14): p. 1311-1320.
- Durie, B.G.M., et al., Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. The Lancet. 2017; 389(10068): p. 519-527.
- Fonseca, R., et al., Clinical and biologic implications of recurrent genomic aberrations in myeloma. Blood. 2003. 101(11): p. 4569-75.
- Boyd, K.D., et al., A novel prognostic model in myeloma based on co-segregating adverse FISH lesions and the ISS: analysis of patients treated in the MRC Myeloma IX trial. Leukemia. 2012; 26(2): p. 349-55.
- Narita, T., et al., t(14;16)-positive multiple myeloma shows negativity for CD56 expression and unfavorable outcome even in the era of novel drugs. Blood Cancer J. 2015. 5: p. e285.

Methods

Databases of three different institutions were utilized in this analysis. Patients diagnosed between December 2006 and March 2017 with t(14;16) by FISH were pooled together and analyzed.

Clinical Characteristics

Patient Characteristics	N=123	First-line Treatments	N=123
Age, median (range)	66 years (38-87)	Induction therapy	
Sex		Immunomodulatory drug based • Lenalidomide • Thalidomide	
• Male	57 (46%)		
• Female	66 (54%)		
Isotype		Proteasome inhibitor based • Bortezomib • Carfilzomib	
• IgG	67 (54%)		
• IgA	32 (26%)		
• FLC	23 (19%)	Proteasome inhibitor plus Immunomodulatory drug	
• Non-secretory	1 (1%)		
ISS			
• 1	25 (20%)	Chemotherapy	
• 2	41 (33%)		
• 3	53 (43%)		
• NA	4 (3%)	Autologous stem cell transplant	
Bone marrow plasma cells, median (range)	60% (0-100)		
Monoclonal protein, median (range)	3.3 gr/dl (0-11.6)		
Hemoglobin, median (range)	10 gr/dl (5.2-15.6)	Maintenance	
Platelets, median (range)	174 x 10 ⁹ /mm ³ (31-426)		
Calcium > upper level of normal	12 (17%)		
Serum Creatinine ≥ 2 mg/dl	16 (12%)	Maintenance	
FISH			
• Deletion 13q	87 (71%)		
• Deletion 17p	27 (22%)		
• Amplification 1q	33 (27%)		
• translocation(4;14)	14 (11%)		
• translocation(11;14)	6 (5%)		

FLC, free light chain; ISS, international staging system; NA, not available; FISH, fluorescent in situ hybridization;

Outcomes

Overall Population

Outcomes by Response to Induction Therapy

Response	Number of patients
sCR	6 (5%)
CR	18 (15%)
VGPR	31 (25%)
PR	44 (36%)
SD	14 (11%)
PD	6 (5%)
NA	4 (3%)
ORR	99 (80%)
$\geq$ CR	24 (20%)

sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate;

Transplant-Eligible Patients

Maintenance Therapy

Prognostic Factors

	Univariate				Multivariate			
	PFS		OS		PFS		OS	
	HR	p-value	HR	p-value	HR	p-value	HR	p-value
Calcium > ULN	2.9	0.006	5	<0.001	1.8	0.11	3.5	0.005
B2M > 5.5 mg/dl	2	0.002	2	0.009	1.6	0.03	1.5	0.15
LDH > ULN	1.85	0.03	3	<0.001	2	0.03	2.3	0.02
1+ abnormality by FISH*	1.9	0.07	1.1	0.8	0.92	0.83	0.6	0.2
CR1	0.29	<0.001	0.56	0.1	0.27	<0.001	0.45	0.04

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; ULN, upper level of normal; B2M, beta-2-microglobulin; LDH, lactic dehydrogenase; FISH, fluorescent in situ hybridization; CR1, complete response at first line.

* Including del17p, t(4;14) and gain 1q.

Conclusions

- In this large cohort of NDMM patients harboring t(14;16), almost all patients (99%) were exposed to novel agents (thalidomide, lenalidomide, bortezomib, carfilzomib, and ixazomib) as part of their upfront treatment.
- t(14;16) myeloma frequently presents with high-risk features, such as ISS Stage 3 disease (53%) and additional cytogenetic abnormalities (82%).
- Despite the wide use of novel agents, ASCT and maintenance, median PFS (19 months) and OS (53 months) of the overall population remain poor.
- In transplant-eligible patients, upfront ASCT prolonged median PFS (31 vs. 10 months) and OS (58 vs. 34 months) compared with no transplant.
- Continuous treatment (maintenance) also prolonged median PFS (36 vs. 19 months) versus no maintenance, without a significant improvement in OS.