Outcomes of high, t(11;14), and standard cytogenetic risk multiple myeloma following early high dose therapy and autologous hematopoietic cell transplantation (SCT)

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Abstract

Background
Current cytogenetic risk stratification in newly diagnosed multiple myeloma (NDMM) is not derived from recent patients (pts) treated with novel agents. High dose melphalan and SCT is a preferred management strategy for transplant eligible NDMM pts following novel agent induction. We investigated outcomes of high cytogenetic risk (HR), t(11;14), and standard cytogenetic risk (SR) NDMM treated with early SCT.

Methods
Following Mayo Clinic IRB approval and in accordance with the Declaration of Helsinki, all pts treated at Mayo Clinic Rochester with SCT for NDMM between 2003 and 2012 were identified (n=941). We excluded pts without FISH cytogenetics from diagnosis (dx) and those who did not undergo SCT within 12 months of dx. HR was defined as del(17p), t(4;14), t(14;20) or t(14;16). Response and progression were defined per IMWG criteria. Overall survival (OS) and progression free survival (PFS) were calculated from dx or SCT.

Results
The study cohort had 409 pts [SR=244, t(11;14)=69, HR=96], with a median estimated follow up of 43 months from dx. Novel agents (IMiDs or proteasome inhibitors) were used in 95% of pts prior to SCT, and 80% of pts achieved partial response. Median PFS for HR, t(11;14), and SR pts was 24.9 (23,30), 28.1 (21,31), and 30.4 (28-34) months respectively (p=0.034). Median OS for HR, t(11;14), and SR pts was 60.5 (46,71), 73.4 (54,89), and 103 (98,113) months respectively (p <0.0001). When only pts who received post SCT maintenance therapy were evaluated (IMiDs or proteasome inhibitors), there was no difference in OS at 5 years from dx between HR and SR pts treated with early SCT (p=0.19).

Conclusions
Following novel agent induction and early SCT, pts with t(11;14) NDMM have inferior OS compared to a SR cohort of similarly treated pts. This is contrary to the current classification scheme. HR pts have similar OS at 5 years from dx compared to SR pts with the use of early SCT and maintenance therapy.

Background

-- Early high dose therapy consisting of novel agent inclusive induction regimens and autologous SCT is a preferred management strategy for transplant eligible patients with NDMM.

-- FISH based cytogenetic risk stratification is still the most common mechanism for classifying NDMM patients into high risk categories.

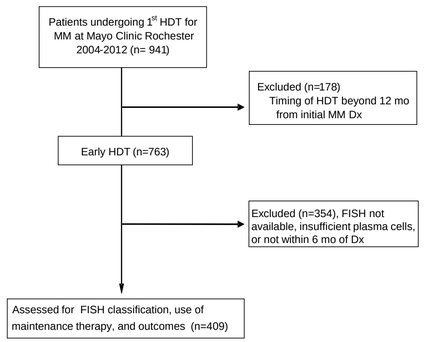
-- Current risk stratification schemes are derived in large part from patients who did not receive novel agent induction and early HDT.

-- There is little known regarding the influence of post HDT maintenance therapy with IMiDs or proteasome inhibitors on distinct FISH categories in the context of early HDT.

-- Classically, t(11;14) has been considered a marker of standard risk disease, where as t(4;14) and del(17p) have been considered markers of intermediate/high and high risk disease respectively.

- We sought to examine the historical risk classification of chromosome 14 translocations (particularly t(11;14) and del(17p) identified by FISH in NDMM in the context of early HDT. We also sought to examine the efficacy of maintenance therapy, in the context of historical risk groups undergoing early HDT.

Patient inclusion

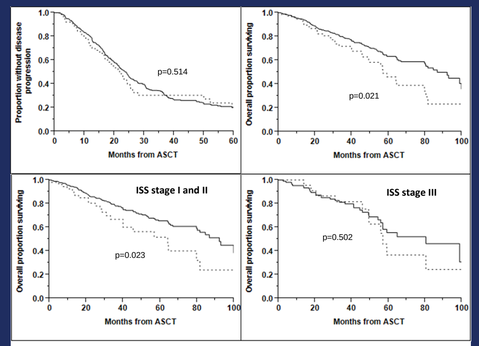


Patient characteristics n=409

Variable	(%)	Median (range)
Age at diagnosis	---	59 (23-75)
Male gender	61	---
Duration: diagnosis to HDT, months	---	5.9 (5.1-7.1)*
B_2-microglobulin, mg/dL	---	3.9 (1.1-48.3)
ISS stage 3	25.9	
Creatinine, mg/dL	---	0.9 (0.5-9.2)
Myeloma bone disease	86	---
Hemoglobin at diagnosis	---	11 (9.3-12.4)*
Serum M protein, g/dL	---	0.5 (0.0-5.7)
Bone marrow plasma cell %	---	5.0 (0.4-94.0)
Plasma cell labeling index (PCLI) %	---	0.0 (0.0-32.3)
Abnormal 14q32(5'IGH3'IGH)	49.4	---
t(4;14)	10.0	---
t(11;14)	19.1	---
t(6;14)	0.5	---
t(14;16)	3.2	---
t(14;20)	1.2	---
t(14;undefined)	15.4	---
del(17p) or monosomy 17	12.2	---
Induction regimen		
RD	43.0	---
RVD	17.6	---
VD	11.7	---
CyBor-D	11.5	---

"R" lenalidomide; "D" dexamethasone; "V/Bor" bortezomib; "Cy" cyclophosphamide

PFS and OS for t(11;14)



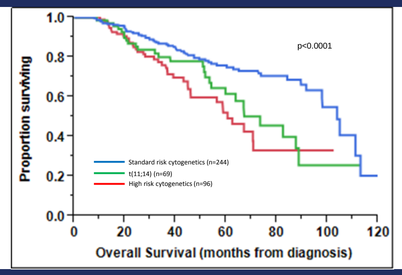
Patients with t(11;14) at diagnosis have inferior OS even among ISS stage 1 and 2 patients despite no difference in PFS as compared to a general cohort of NDMM pts treated with early HDT.

= t(11;14)
= General cohort

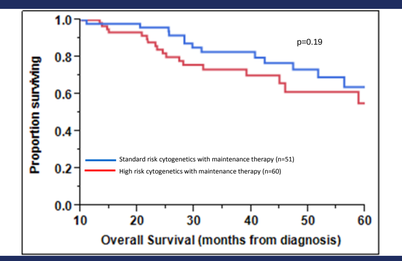
Multivariate analysis of outcomes following early HDT

Variable	n (=409 total)	PFS HR	PFS 95% CI	PFS P-value	OS HR	OS 95% CI	OS P-value
HR FISH	96	1.6	1.2-2.1	0.003*	2.1	1.4-3.2	0.001*
t(11;14)	69	1.1	0.8-1.5	0.558	2.0	1.3-3.0	0.002*
Relapsed disease at time of early HDT	34	1.5	1.0-2.2	0.040*	1.8	1.1-2.9	0.027*
Post HDT maintenance therapy	124	0.6	0.5-0.9	0.004*	1.1	0.7-1.7	0.561
ISS stage III	106	1.3	1.0-1.6	0.101	1.0	0.7-1.5	0.995

OS for HR, t(11;14), and SR NDMM post early HDT



OS for HR and SR NDMM with post early HDT + maintenance



Discussion

- Strengths of our study include the relatively homogenously treated population (all pts received novel induction and early HDT), with FISH data available from near the time of diagnosis.
- Recent data out of the MD Anderson Cancer Center Myeloma group have also suggested inferior outcomes for t(11;14) disease compared to a standard cytogenetic risk cohort.
- Median PFS and OS for t(11;14) and SR pts was longer in our data compared to historical comparison cohorts of pts not homogenously receiving novel agent induction and early HDT.

Conclusions

- The results from our current study call into question the "standard-risk" assignment of t(11;14) disease in the setting of novel induction and early HDT, suggesting that the t(11;14) abnormality should be in the intermediate risk group.
- The application of maintenance therapy in HR patients seems to be validated as these patients had non-inferior overall survival at 5 years when compared to SR patients who also received post HDT novel-agent maintenance therapy