Impact of Autologous Transplantation in Patients with Multiple Myeloma with t(11;14): A Propensity-Score Matched Analysis

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Abstract

Purpose: Patients with multiple myeloma with t(11;14) have been considered to have standard-risk disease. However, several recent reports have shown contradictory results. We identified 95 patients with multiple myeloma with t(11;14) on FISH studies, who underwent upfront autologous hematopoietic stem cell transplant (auto-HCT) at our center. We compared their outcome with a group of standard-risk patients with multiple myeloma who had diploid cytogenetics by both conventional cytogenetics (CC) and FISH (n = 287).

Experimental Design: To reduce the bias between the groups, we performed a 1:1 propensity score matching technique for analysis. A total of 160 patients, 80 in each group, were identified. Patients in the 2 groups were matched for age, International staging system stage at diagnosis, serum creatinine at presentation, disease status at auto-HCT, type of preparative regimens, dose of melphalan used for conditioning, and induction and maintenance regimens.

Results: Patients in t(11;14) group had a post-auto-HCT overall response rate (ORR) of 97.5% (78/80), compared with 100% (80/80) in the standard-risk control group (P = 0.50). Complete response rate in the t(11;14) group was 35% (28/80), compared with 45% (36/80) in the standard-risk control group (P = 0.26). The 4-year PFS rates were 40.8% (95% CI, 29.6%–56.1%) and 51.1% (95% CI, 39.4%–66.3%) in the t(11;14) and standard-risk control groups, respectively (P = 0.14). The 4-year OS rates were 74.9% (95% CI, 63.3%–88.7%) and 88.3% (95% CI, 80.4%–97.0%) in the t(11;14) and standard-risk control groups, respectively (P = 0.12).

Conclusions: Our study confirms that t(11;14) multiple myeloma undergoing upfront autologous transplantation had similar outcomes as patients with multiple myeloma with normal cytogenetic and FISH studies. Existence of additional genomic aberrations by CC or FISH was associated with a worse outcome.

Introduction

Multiple myeloma, a plasma cell neoplasm, is characterized by cytogenetic abnormalities that are not only relevant to disease biology and prognosis, but may also play a role in therapeutic decision making (1). The most common primary oncogenic events in multiple myeloma are either Immunoglobulin heavy chain gene (IgH) locus translocations or hyperdiploidy, involving odd-numbered chromosomes. The IgH translocations include t(4;14), t(11;14), t(14;16), t(14;20), and t(6;14), with t(11;14) being the most common translocation with a reported frequency of 15% to 20% (1–3). As multiple myeloma evolves, abnormal plasma cell clones acquire secondary abnormalities, such as copy number alterations (1p deletion, 1q gain, 17p loss) and/or other genetic mutations, which can alter the disease biology, drive clonal progression, and influence clinical outcomes (4).

Traditionally, patients with multiple myeloma with t(11;14) have been considered to have standard-risk disease. However, a few recent reports have challenged this notion (3, 5, 6). Several factors could explain the disparate outcomes in t(11;14) in multiple myeloma. For instance, the inclusion of patients with t(11;14) on both FISH testing and CC analysis may be partly responsible for this discrepancy. That is because abnormalities on CC analysis represent high proliferation rates in clonal plasma cells and portend poor survival. Second, concurrent high-risk...
genetic abnormalities besides t(11;14) may increase the risk of progression with worse survival outcomes. The variable incidence of these high-risk (HR) abnormalities in different studies may have contributed to different outcomes. Finally, most of these studies were retrospective analyses with inherent limitations and heterogeneous populations, which may have also contributed to diverse outcomes in these studies.

The propensity-score matching in observational studies may overcome some of these limitations. We previously reported the impact of t(11;14) on the outcomes of patients with multiple myeloma who underwent autologous hematopoietic stem cell transplantation (auto-HCT) at our institution in a small cohort of patients (6, 7). To overcome some of the limitations explained above, we designed this study with a larger cohort. The primary aim was to compare the outcomes of patients with multiple myeloma with t(11;14) to a propensity-score matched control group of patients with MM with normal diploid cytogenetics and normal FISH analysis.

Materials and Methods

Patients

We performed a retrospective chart review on patients with symptomatic multiple myeloma who underwent upfront high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (auto-HCT) at the UT MD Anderson Cancer Center (MDACC) between January 2006 and December 2015. The study does not include patients with multiple myeloma who were transplant-ineligible, or those who were transplant-eligible but were not referred for an auto-HCT. A total of 1,491 patients with multiple myeloma met these criteria. Of these, 837 (56.1%) patients had available data for both CC and FISH at any time from diagnosis to auto-HCT. Patients who had missing data for either CC or FISH, and those where t(11;14) was detected by CC only, were excluded from the analysis. From these 837 patients, 3 exclusive groups were created for propensity match analysis: (i) t(11;14) group where t(11;14) abnormality was detectable by FISH (n = 95); (ii) standard-risk multiple myeloma control group of patients with normal diploid CC and absence of any abnormalities either by FISH or CC (n = 287); and (iii) high-risk (HR) multiple myeloma control group of patients with presence of one or more known HR abnormalities such as 17p deletion, t(4;14), t(14;16), t(14;20), and 1q gain by either CC or FISH (n = 154; ref. 8).

The t(11;14) group was further divided into 3 subgroups: (i) t (11;14)-alone: presence of t(11;14) without any other abnormalities detected by FISH or CC; (ii) t(11;14) + HR: t(11;14) with presence of one or more known HR abnormalities as defined above; (iii) t(11;14) + NHR: t(11;14) with presence of other non-HR abnormalities. In the t(11;14) group, a total of 44 patients had no other abnormalities, 23 patients had concurrent HR abnormalities, and 28 had concurrent non-HR abnormalities. Clinical characteristics, pretreatment laboratory parameters, International Staging System (ISS) stage, treatment administered, responses, and outcomes were collected from a retrospective chart review under an Institutional Review Board (IRB)-approved protocol with waiver of informed consent. The study was conducted according to the Declaration of Helsinki, and the Health Insurance Portability and Accountability Act guidelines of 1996.

Objectives and definitions

The primary objective of our study was to compare the survival outcomes of FISH-positive t(11;14) multiple myeloma group to a standard-risk multiple myeloma control group. The secondary objective of the study was to evaluate the impact of various other coexistent abnormalities in t(11;14) group on survival outcomes and compare these subgroups to propensity-matched similar control groups of standard and/or high-risk MM patients. Diagnosis of multiple myeloma, clinical response, relapse and progression were defined by the International Myeloma Working Group (IMWG) criteria (9). Progression-free survival (PFS) time was defined as the duration from the date of transplant to the date of progression or death, whichever was earlier. Overall survival (OS) time was defined as the duration from the date of transplant to the date of death or the date of last-follow-up if patients were alive. Lost to follow-up patients were censored alive at the time of their last follow-up.

Cytogenetics and FISH analyses

Conventional chromosomal analysis was performed on G-banded metaphases prepared from bone marrow (BM) aspirate cultured for 24 hours without mitogen and 72 hours with mitogen of lipopolysaccharides. A total of 20 metaphase cells were analyzed. A CC abnormality was considered positive if it was present in 2 or more cells with gain of chromosome or chromosomal structural abnormality(ies), and in 3 or more cells with loss of chromosome. The FISH analysis for t(11;14)/IGH/CCND1 was performed on cultured cells or CD138 enriched cells (when BM plasma cells were between 3% and 15%) using LSI IGH/CCND1 XT dual color, dual fusion translocation probes from Abbott Molecular, Inc., a total of 200 interphase with round nuclei were analyzed. The normal cut off for IGH/MYEOV/CCND1 rearrangement established at 95% (P < 0.05) confidence level in the MDACC Cytogenetics Laboratory is 0.4%. In addition, 4 more
FISH analysis including TP53/CEP17, IGH/FGFR3, CDKN2C/CKS1B, and RB1/13q34 were included in myeloma work-up.

Statistical methods

Among the t(11;14) and standard-risk control group, data for creatinine were missing in 26 patients and for induction in 5 patients. These patients were excluded leaving a total of 351 patients, 89 patients in t(11;14) group and 262 patients in the standard-risk control group that were used for statistical matching. From these 351 patients, a total of 80 matched pairs, t(11;14) and standard-risk control, were created via 1:1 propensity-score matched control without replacement.

Furthermore, the t(11;14) cohort was divided into 3 subgroups: t(11;14)-alone, t(11;14) + HR, t(11;14) + NHR, which were compared separately to control cohorts (standard or high risk) via propensity-score matched analysis. Variables included in the propensity-score matched analysis were age, ISS stage at diagnosis, serum creatinine at presentation, disease status at auto-HCT, type of preparative regimens, dose of melphalan used for conditioning and induction/maintenance chemotherapies used for treatment. We used the linear logit propensity score as the distance measure and set the caliper of 0.2 standard deviations of the propensity score (10). The balance was verified by assessing standardized mean differences between groups for all variables in the matched cohort. A cut-off value of <25% was used to check covariate balance. Categorical covariates were summarized by frequencies and percentages, and continuous covariates were summarized by means, standard deviations, medians, and ranges. Unadjusted survival distributions were estimated by the Kaplan–Meier (KM) method and compared using the stratified log-rank test on matched pairs (10, 11).

Comparisons of categorical outcomes between matched pairs were evaluated using Fisher exact tests or McNemar tests. All statistical analyses were performed using R version 3.5.1. All statistical tests used a significance level of 5%. No adjustments for multiple testing were made.

Results

Primary analysis
t(11;14) versus standard-risk control group. Patient characteristics.

Baseline patient characteristics are summarized in Table 1. Patients in both groups were matched for age, ISS stage at diagnosis, serum creatinine at presentation, disease status at auto-HCT, type of preparative regimens, dose of melphalan used for conditioning, and induction and maintenance regimens. Baseline characteristics and summary of survival outcomes for the whole unmatched population (n = 351) of t(11;14) and the standard-risk control group is available in the supplementary file (Supplementary Tables S1 and S2; Supplementary Figs. S1 and S2). Other concurrent cytogenetic abnormalities in the t(11;14) group are described in Supplementary Table S3.

Induction regimen. A total of 78/80 (97.5%) and 79/80 (98.7%) patients received induction therapy with immunomodulatory drugs (IMiD) and/or proteasome inhibitors (PI) in the t(11;14) and the control group, respectively (Table 1). The use of IMiD-PI-dexamethasone combination as induction was the same in both groups at 60% (48/80). Overall response rate (ORR) before auto-HCT was 93.7% (75/80) in both groups. The number of patients with complete response (CR), very good partial response (VGPR), and partial response (PR) was 5 (6.2%), 23 (28.7%) and 47 (58.8%), respectively, in the t(11;14) group, and 5 (6.2%), 28 (35.0%) and 42 (52.5%), respectively, in the control group.

Preparative regimen and maintenance therapy. Melphalan alone was used as preparative regimen in 74 (92.5%) and 73 (91.2%) patients in t(11;14) and control groups, respectively (Table 1). The combination of Busulfan and melphalan was used as preparative regimen in 6 (7.5%) and 7 (8.8%) patients in the t(11;14) and control groups, respectively.

Overall, 64 (80%) and 68 (85%) patients received maintenance therapy in t(11;14) and control groups, respectively. In the t(11;14) group, maintenance therapy with either IMiDs or PI was used in 48 (60%) and 4 (5%) patients, respectively (Table 1). The corresponding number of patients for the control group were similar at 45 (56.2%) and 3 (3.8%), respectively. The combination of IMiDs and PI for maintenance was used in 11 (13.8%) patients in both groups. Moreover, maintenance with lenalidomide and elotuzumab combination was used in 5 (6.2%) patients in both groups.

Response post-auto-HCT. Patients in the t(11;14) group had an ORR post-auto-HCT of 97.5% (78/80), compared with 100% (80/80) in the standard-risk control group (P = 0.50; Table 2). CR rate

<table>
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<tr>
<th>Variable</th>
<th>Overall (n = 160), n (%)</th>
<th>Control (n = 80), n (%)</th>
<th>t(11;14) (n = 80), n (%)</th>
<th>Std mean diff</th>
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<tr>
<td>Age, mean (SD)</td>
<td>60.5 (9.9)</td>
<td>60.7 (10.0)</td>
<td>60.3 (9.9)</td>
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<td>ISS Stage</td>
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<td>I</td>
<td>64 (40.0)</td>
<td>32 (40.0)</td>
<td>32 (40.0)</td>
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<tr>
<td>II</td>
<td>44 (27.5)</td>
<td>22 (27.5)</td>
<td>22 (27.5)</td>
<td>0.000</td>
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<tr>
<td>III</td>
<td>34 (21.2)</td>
<td>17 (21.2)</td>
<td>17 (21.2)</td>
<td>0.000</td>
</tr>
<tr>
<td>Unknown</td>
<td>18 (11.2)</td>
<td>9 (11.2)</td>
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<tr>
<td>Creatinine, mean (SD)</td>
<td>144 (129)</td>
<td>134 (129)</td>
<td>153 (146)</td>
<td>0.116</td>
</tr>
<tr>
<td>Response prior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>10 (6.2)</td>
<td>5 (6.2)</td>
<td>5 (6.2)</td>
<td>0.000</td>
</tr>
<tr>
<td>VGPR</td>
<td>51 (31.9)</td>
<td>28 (35.0)</td>
<td>23 (28.7)</td>
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<td>PR</td>
<td>89 (55.6)</td>
<td>42 (52.5)</td>
<td>47 (58.8)</td>
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<td>PD</td>
<td>6 (3.8)</td>
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<td>4 (5.0)</td>
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<td>SD</td>
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<td>BuMel</td>
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<td>Melphalan, Maintenance, n (%)</td>
<td>147 (91.9)</td>
<td>73 (91.2)</td>
<td>74 (92.5)</td>
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<td>IMiD</td>
<td>93 (58.1)</td>
<td>45 (56.2)</td>
<td>48 (60.0)</td>
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<tr>
<td>No maintenance</td>
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<td>16 (20.0)</td>
<td>12 (15.0)</td>
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</tr>
<tr>
<td>PI + IMiD</td>
<td>22 (13.8)</td>
<td>11 (13.8)</td>
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</tr>
<tr>
<td>IMiD + Elotuzumab</td>
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<td>5 (6.2)</td>
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</tr>
<tr>
<td>Velcade</td>
<td>7 (4.4)</td>
<td>3 (3.8)</td>
<td>4 (5.0)</td>
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<td>Induction, n (%)</td>
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<td></td>
<td></td>
<td></td>
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<td>IMiD-based</td>
<td>15 (9.4)</td>
<td>8 (10.0)</td>
<td>7 (8.8)</td>
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</tr>
<tr>
<td>Other</td>
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<td>1 (1.2)</td>
<td>2 (2.5)</td>
<td>0.069</td>
</tr>
<tr>
<td>PI + IMiD-based</td>
<td>96 (60.0)</td>
<td>48 (60.0)</td>
<td>48 (60.0)</td>
<td>0.000</td>
</tr>
<tr>
<td>VCD</td>
<td>29 (18.1)</td>
<td>14 (17.5)</td>
<td>15 (18.8)</td>
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<td>VD</td>
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<td>8 (10.0)</td>
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<td></td>
</tr>
<tr>
<td>200 mg/m²</td>
<td>124 (77.5)</td>
<td>61 (76.2)</td>
<td>63 (78.8)</td>
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<tr>
<td>140 mg/m²</td>
<td>36 (22.5)</td>
<td>19 (23.8)</td>
<td>17 (21.2)</td>
<td>-0.059</td>
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</tbody>
</table>

Abbreviations: BuMel, Busulfan plus melphalan; C, cyclophosphamide; D, dexamethasone; PI, proteasome inhibitors; SD, stable disease; V, bortezomib; Std mean diff, standardized mean difference.
in the t(11;14) group was 35% (28/80), compared with 45% (36/80) in the control group (P = 0.26).

Survival. The median follow-up time for the matched cohort was 42.7 (range 2.9–111.6) months. The median PFS was 29.9 (95% CI, 25.8–not reached) months and 51.9 (95% CI, 36.0–not reached) months for the t(11;14) and the standard-risk control group, respectively (P = 0.14; Fig. 1). The 4-year PFS rates were 40.8% (95% CI, 29.6%–56.1%) for the t(11;14) and 51.1% (95% CI, 39.4%–66.3%) for the standard-risk control group. The median OS was not reached for both t(11;14) and the control group (P = 0.17; Fig. 2). The 4-year OS rates were 74.9% (95% CI, 63.3%–88.7%) and 88.3% (95% CI, 80.4%–97.0%) for the t(11;14) and the control group, respectively.

Secondary subgroup analyses
t(11;14)-alone versus standard-risk control group. To minimize the impact of concurrent cytogenetic abnormalities on the outcomes, we selected patients with t(11;14) as the only chromosomal abnormality on FISH studies. From the 2 groups, t(11;14)-alone and standard-risk control group, a total of 39 matched pairs [39/44 t(11;14)-alone patients, 88.6%] were created. Both groups were well matched as shown in Supplementary Table S4. Patients in the t(11;14)-alone group had an ORR post-auto-HCT of 100%, with rates of CR, VGPR, and PR at 25.6%, 53.8%, and 20.5%, respectively. In the standard-risk control group, the ORR was also 100% with rates of CR, VGPR, and PR at 43.6%, 46.2%, and 10.3%, respectively.

Figure 1. Kaplan–Meier plots of the PFS for matched cohort of t(11;14) patients with multiple myeloma (n = 80, number of progression or death = 39) versus standard-risk control patient with multiple myeloma (n = 80, number of events = 36).

Figure 2. Kaplan–Meier plots of the overall survival for matched cohort of t(11;14) patients with multiple myeloma (n = 80, number of deaths = 14) versus standard-risk control multiple myeloma group (n = 80, number of deaths = 16).

The median follow-up time for this cohort was 41.9 (range 12.3–111.6) months. The median PFS was not reached for the t(11;14)-alone group, and 44.6 (95% CI, 37.1–not reached) months for the standard-risk control group (P = 0.37; Fig. 3). The 4-year PFS rates were similar at 52.2% (95% CI, 36.4%–75.0%) and 47.3% (95% CI, 30.9%–72.4%) for the t(11;14)-alone and the standard-risk control group, respectively. The median OS time was not reached for t(11;14)-alone group, and 81.1 months for the standard-risk control group (P = 1.00; Fig. 4). The 4-year OS rates were similar at 91.8% (95% CI, 81.0%–100%) for the t(11;14)-alone group and 93.6% (95% CI, 85.4%–100%) for the control group.

t(11;14) + other concurrent cytogenetic abnormalities versus standard-risk control group. We also compared t(11;14) patients with concurrent cytogenetics abnormalities (both HR and NHR) to a propensity-score matched standard-risk control group (43 matched pairs). Patient characteristics are detailed in Supplementary Table S5. The median follow-up time for this cohort was 41.6 (range 2.9–78.8) months. A statistically significant difference in PFS (P = 0.028; Supplementary Fig. S3), but not in OS (P = 0.08; Supplementary Fig. S4) was observed between the 2 groups. The 4-year PFS rate in the combined HR and NHR group was significantly worse at 31.3% (95% CI, 18.3%–53.6%), compared with 55.0% (95% CI, 38.6%–
In this study, using propensity-score matched analysis, we showed that patients with multiple myeloma with t(11;14) on FISH had similar PFS and OS compared with standard-risk control multiple myeloma group (n = 39, number of deaths = 2) versus standard-risk control multiple myeloma group (n = 39, number of deaths = 6).

78.3% in the standard-risk control group. The 4-year OS rate in combined HR and NHR group was significantly worse at 62.0% (95% CI, 44.8%–88.9%) compared with 90.6% (95% CI, 81.0%–100%) in the standard-risk control group.

t(11;14) + HR versus high-risk control group. To evaluate if the presence of t(11;14) alters outcomes of HR cytogenetics, we also compared t(11;14) + HR group to a propensity-score matched high-risk control group (20 matched pairs). Patient characteristics are detailed in Supplementary Table S6. The median follow-up time for this cohort was 26.4 (range 2.9–72.0) months. The median PFS for the t(11;14) + HR group and the high-risk control group were similar at 25.1 months (95% CI, 21.1–not reached) and 30.2 months (95% CI, 25.0–not reached), respectively (P = 0.48; Supplementary Fig. S5).

The 3-year PFS rates were 11.4% (95% CI, 1.9%–68.8%) and 30% (95% CI, 12.2%–74%) for the t(11;14)-HR and the high-risk control group, respectively. The 3-year OS rates were 69.6% (95% CI, 47.5%–100%) and 79.7% (95% CI, 63.7%–99.6%) for the (11;14)-HR group and the high-risk control group, respectively (P = 0.69; Supplementary Fig. S6).

Discussion

In this study, using propensity-score matched analysis, we showed that patients with multiple myeloma with t(11;14) on FISH had similar PFS and OS compared with standard-risk patients with multiple myeloma with normal cytogenetics and FISH after an auto-HCT. Notably, FISH-positive t(11;14) patients, who had concurrent cytogenetic abnormalities, either high-risk or non-high-risk, had significantly worse survival outcomes than patients with t(11;14) alone. We also showed that the presence of t(11;14) does not affect the poor survival outcomes of patients with high-risk cytogenetics.

There are contradictory data in multiple myeloma literature on the outcomes of patients with t(11;14). The largest study was recently published from the Mayo Clinic (5), where a group of 365 patients with multiple myeloma with t(11;14) was compared with a heterogeneous control group (n = 730), matched for age and year of diagnosis only, who had abnormalities other than t(11;14). The control group was further divided into 2 subgroups: one with non-t(11;14) translocations (n = 132), and the other with no translocations (n = 598). The median OS in the t(11;14) group was significantly shorter at 74.4 months compared with 103 months in the group with no translocations (P < 0.01). The worse OS in the study could be attributed to the fact that only 60% of the patients received auto-HCT and most patients received only one novel agent-based induction, either a proteasome inhibitor or an immunomodulatory drugs. Also, the information regarding additional high-risk abnormalities, such as gain of 1q, was not reported as it was not a part of the regular FISH panel at the time of the study. In fact, when the analysis was limited to patients with age <65 years, a surrogate for transplant eligibility, without 17p deletion, PFS was similar between t(11;14) and no-translocation arm (28.5 months vs. 32.3 months, P = 0.399). Our patient population was relatively homogenous with all patients receiving upfront autologous transplantation, and the control groups were matched by a propensity-score matching algorithm. Although our results may not apply to transplant-ineligible patients with t(11;14), they do, however, may be used as benchmark for patients with multiple myeloma with t(11;14) receiving upfront auto-HCT, given a relatively large sample size, relatively homogenous population, and propensity matching.

We had previously reported on 993 patients with multiple myeloma who underwent auto-HCT at MDACC (6), with 869 patients with no abnormalities, 27 patients with t(11;14)q(13; q32), and 97 patients with HR abnormalities by CC or FISH studies. Three-year OS for normal, t(11;14)q(13;q32) and HR groups were 83%, 63%, and 34%, respectively (P < 0.00001). When analyzed separately, both t(11;14)q(13;q32) alone and t(11;14)q(13;q32) with other HR abnormalities were predictive of significantly shorter PFS. However, that study had only 27 patients with t(11;14), and included patients with t(11;14) detected on both CC and/or FISH, which may have contributed to the worse outcome in the t(11;14) alone group (12, 13). In this study, we also analyzed the survival outcomes of t(11;14) group when t(11;14) was detected by CC alone with FISH alone (n = 82). As expected, patients with t(11;14) by CC had a significantly worse PFS (median: 22.3 months vs. 37.6 months) and OS (4-year OS of 59.5% vs. 81.4%) compared with FISH positive t(11;14) patients (Supplementary Table S7; Supplementary Figs. S7 and S8). However, this should be interpreted with caution as 11 patients in CC group had missing data on FISH. The difference in outcomes could be attributed to underdiagnosis of concurrent high-risk abnormalities that would have been detected by FISH. Similarly, in another study by Dewald and colleagues (14), 154 patients with multiple myeloma were evaluated by CC and FISH analyses. The presence of t(11;14) by CC was associated with an inferior outcome. However, t(11;14) by FISH was not associated with a worse outcome compared with patients with normal CC and FISH studies.

Several other studies have reported findings that are similar to our study. A recent retrospective analysis from the Japanese Transplant Registry evaluated the impact of auto-HCT in t(11;14) patients with multiple myeloma (15). In this study, 90% of patients with multiple myeloma (n = 97) were treated with novel agents followed by upfront auto-HCT. A total of 45 patients had t(11;14) detected through CC and/or FISH, of which 22 had additional chromosomal abnormalities(ACA). The t(11;14) patients without ACA had significant longer PFS (HR = 0.49; P = 0.029) and OS (HR = 0.27; P = 0.005) than patients with t(11;14) with ACA. However, PFS and OS of the whole t(11;14) cohort (n = 45) was similar to patients with normal karyotype and FISH. In the MRC Myeloma IX trial, thalidomide-containing arm was compared with conventional chemotherapy arm for newly
diagnosed multiple myeloma (12, 13). A total of 127 (17.6%) patients had t(11;14), out of which 36 patients had high-risk abnormalities including +1q and del 17p. The median OS was significantly better in patients with t(11;14) alone (59.2 months), compared with patients with t(11;14) and concomitant 1q or 17p (38.1 months). Similarly, in the Intergroupe Francophone du Myelome trials (2), out of 1,064 patients screened for genomic aberrations by FISH, 154 (21%) patients had t(11;14). Patients were treated with conventional chemotherapy followed by double auto-HCT. The median event-free survival in t(11;14), del17p and t(4;14) was 35, 15, and 20.6 months, respectively. The t (11;14) did not have any impact on OS, whereas del17p and t (4;14) were associated with shorter OS.

Patient outcomes in a study depend upon the complex interplay of multiple factors including demographic features, genomic aberrations, treatment type and intensity, and responses to specific treatment types. One of the strengths of our study is the use of propensity-score matched analysis to compare the 2 cohorts. Propensity score methods minimize bias by balancing covariate distributions of measured covariates between study groups. In this study, patients in both groups received similar induction, conditioning regimens and doses, and maintenance. Moreover, we only included patients who underwent auto-HCT. An inherent limitation of our study is its retrospective nature. The study population does not include transplant-ineligible patients, or the patients not referred to transplant, or patients who progressed after referral. Hence, our results cannot be generalized to patients with newly diagnosed multiple myeloma population with t(11;14). Also, the samples for FISH analysis at our institution were not available for all the patients. Hence, our results cannot be generalized to patients with newly diagnosed multiple myeloma population with t(11;14). Also, the samples for FISH analysis at our institution were not plasma-cells enriched for the majority of cases, which may lead to a lower detection rates, especially when plasma cells were rather sparse in the bone marrow.

In t(11;14), proto-oncogene CCND1 is juxtaposed to the IGH gene, resulting in upregulation of the protein product, cyclin D1, which favors the cell-cycle progression of abnormal plasma cell clones. These plasma cell clones have also been shown to be dependent on anti-apoptotic pathways for their survival (16, 17). In particular, anti-apoptotic BCL-2 protein is overexpressed in patients with t(11;14) (18). Venetoclax, a BCL-2 inhibitor, has shown significant activity in patients with multiple myeloma with t(11;14) (19), and is expected to play an important role in the future treatment of these patients.

In conclusion, our study showed that patients with multiple myeloma with t(11;14), who underwent upfront auto-HCT, had similar outcomes as patients with multiple myeloma with normal cytogenetic and FISH studies. Existence of additional genomic aberrations by CG or FISH was associated with a worse outcome.

Disclosure of Potential Conflicts of Interest

H.C. Lee is a consultant/advisory board member for Takeda Pharmaceutical, Amgen Inc., Janssen Pharmaceuticals, Celgene, and Sanofi, and reports receiving commercial research support from Takeda Pharmaceuticals, Amgen Inc., Janssen Pharmaceuticals, Celgene and GlaxoSmithKline. E.E. Manasanch reports receiving speakers bureau honoraria from Janssen, Celgene and Sanofi, and reports receiving commercial research grants from Janssen, Celgene, Poseida, Takeda and Cellectis, and reports receiving commercial research support from Quest Diagnostics, Sanofi and Merck. K.K. Patel is an employee of and has ownership interests (including patents) at Janssen, Celgene, Pfizer, Takeda, Oncopetides, Nektar, and Bristol-Myers Squibb. R.Z. Orlofski is a consultant/advisory board member for Amgen, Celgene, Ionis, Legend Biotech, Molecular Partners, Sanofi-Aventis, Servier, Takeda Pharmaceuticals North America, and reports receiving commercial research grants from BioTherapyX. No potential conflicts of interest were disclosed by the other authors.

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