Leukemia Research 37 (2013) 1251–1257

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

t(11;14) multiple myeloma: A subtype associated with distinct immunological features, immunophenotypic characteristics but divergent outcome

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ARTICLE INFO

Article history:
Received 17 December 2012
Received in revised form 29 May 2013
Accepted 15 June 2013
Available online 5 August 2013

Keywords:
Multiple myeloma
Chromosome aberration
Fluorescence in situ hybridization
Prognosis
Survival

ABSTRACT

t(11;14)(q13;q32) is the most common chromosome translocation in multiple myeloma (MM), but a consensus of clinicopathological features and impact on survival is yet to be reached. We analyzed a cohort of 350 patients with various plasma cell malignancies, including newly diagnosed MM (NDMM, $n = 253$), relapsed/refractory MM (RRMM, $n = 77$), as well as primary and secondary plasma cell leukemia (PCL, $n = 10$ and $n = 10$, respectively). Results: A remarkably higher frequency of t(11;14) was observed in the PCL than in the NDMM. A high incidence of t(11;14) was detected in the IgD, IgM, and nonsecretory MM. The t(11;14) MM group was associated with a significantly higher positive rate of B-lineage associated antigens CD20 and CD79a as well as the lack of CD56 expression. t(11;14) was less likely to be accompanied by 13q14 deletion than 13q14 deletion frequency in non-t(11;14) population ($p = 0.026$), and fewer patients displaying t(11;14) were identified as belonging to the high-risk cytogenetic group due to the extremely low incidence of t(4;14) and t(14;16). As a whole, patients exhibiting t(11;14) had a comparable outcome with the control cohort in NDMM, but CD20 was able to identify two subsets of the disease with dissimilar outcomes. Among patients receiving bortezomib-based treatment, patients harboring t(11;14) without CD20 expression had a significantly shortened PFS (11.0 versus 43.0 months, $p = 0.005$) and OS (16.5 versus 54.0 months, $p = 0.016$) compared with patients displaying t(11;14) with CD20. Our findings suggest that although the t(11;14) plasma cell disorder displayed distinct biological, clinical and laboratory features, it was a heterogeneous disease with divergent outcome.

1. Introduction

Multiple myeloma (MM) is heterogeneous with respect to clinical presentation, subsequent responsiveness to chemotherapy, and long-term survival [1]. Current data support the hypothesis that pivotal genetic events are the culprits of the pathogenesis of this disease and the source of the heterogeneity [2]. It has been considered that MM is not a single disease, but rather a group of disorders, which were best discerned according to the underlying cytogenetic aberrations. The specific cytogenetic abnormalities have distinct association patterns in patients with MM, allowing for the cytogenetic subclassification of the disease.

The t(11;14)(q13;q32) is the most common chromosome translocation in MM, with an occurrence rate of 15–18% [3]. As a unique subtype, the t(11;14) plasma cell disorder is surrounded by many controversies. For example, t(11;14)(q13;q32) can lead to the up-regulation of cyclinD1 with presumptive signals promoting cell proliferation; however, patients harboring t(11;14) showed a significantly decreased proliferative index as evaluated by multiparameter flow cytometry [4]. Although a number of distinct clinicopathological features have been attributed to t(11;14) MM [5–7], many questions remain unanswered, especially for the prognostic value of t(11;14).

To address this issue, we analyzed a cohort of 350 patients with various plasma cell disorders, including the newly diagnosed MM (NDMM), relapsed/refactory MM (RRMM), primary plasma cell leukemia (pPCL), and secondary plasma cell leukemia (sPCL), who had complete FISH studies available. The prevalence of t(11;14) was detected in different type of plasma cell dyscrasias, and the baseline characteristics and clinical outcomes of t(11;14) MM were

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http://dx.doi.org/10.1016/j.leukres.2013.06.020

compared with the control cohort. Our study demonstrates that a remarkably higher frequency of t(11;14) was observed in the PCL than in the NDMM. t(11;14) was more common in the IgD, IgM, and nonsecretory MM with frequent expression of antigens such as CD20 and CD79a. Myeloma patients exhibiting t(11;14) could be divided into two groups according to the expression of CD20: patients lack of CD20 expression has significantly shortened survival in bortezomib-based treatment group.

2. Materials and methods

2.1. Patients and treatment

We identified 350 patients with plasma cell dyscrasias between January 2004 and December 2012, with a median follow-up of three years. These patients included 253 NDMM cases, 77 RRMM cases, 10 pPCL cases and 10 sPCL cases. All the patients had complete FISH studies available. Patients were classified as MM and PCL according to the International Myeloma Working Group (IMWG) [8].

According to their request, patients were assigned to either the thalidomide-based or bortezomib-based treatment: 106 patients with symptomatic MM were treated with thalidomide-based chemotherapy, such as TAD (thalidomide 200 mg/day; Adriamycin 9 mg/m^2, administered intravenously on days 1–4; and dexamethasone 20 mg/d orally or intravenously, on days 1–4 and 9–12), TCD (thalidomide 200 mg/day; cyclophosphamide 300 mg/m^2, intravenously, on days 1 and 8; and dexamethasone 20 mg/d orally or intravenously, on days 1–4 and 9–12). 147 myeloma patients received bortezomib-based therapy, BCD (bortezomib 1.3 mg/m^2, intravenously, on days 1, 4, 8, and 11; cyclophosphamide 300 mg/m^2, intravenously, on days 1 and 8; and dexamethasone 20 mg/d, orally or intravenously, on days 1, 2, 4, 5, 8, 9, 11, and 12) or PAD (bortezomib 1.3 mg/m^2, intravenously, on days 1, 4, 8, and 11; Adriamycin 9 mg/m^2, intravenously on days 1 to 4; and dexamethasone, 20 mg/d orally or intravenously, on days 1, 2, 4, 5, 8, 9, 11, and 12). After at least four cycles of treatment with partial remission or better, patients underwent consolidation therapy, which was either autologous stem cell transplant (ASCT) or chemotherapy with the patient's original regimen according to the their request. Subsequently, patients were treated with thalidomide (100–150 mg/day) for 1 year to maintain the response. When necessary, some of them also received supportive treatment with zoledronic acid every 1–2 months and erythropoietin or granulocyte colony-stimulating factor. All patients underwent prophylactic acyclovir treatment. Among the patients receiving thalidomide-based treatment, 20 patients underwent ASCT. In the bortezomib group 22 patients received ASCT therapy.

2.2. Detection of molecular cytogenetic aberrations by fluorescence in situ hybridization (FISH)

All the MM samples were purified using the Miltenyi technology (anti-CD138–coated magnetic beads; Paris, France), as previously reported[3]. Del(13q) abnormality was analyzed with the probe specific for the 13q34 locus (LSI 13q34, Abbott Laboratories). Del(17p13) was assessed using a probe specific for the 17p13.1 locus (LSI p53, Abbott Laboratories). To detect the 1q21 amplification, we used the 1q21 (CKS1B) probe (GP Medical Technologies, Beijing, China). The LSI IGH/FGFR3 dual-color probe (Abbott Laboratories) was used to detect t(4;14), LSI IGH/CCND1 (Abbott Laboratories) XT to t(11;14), and IGH/MAF DF to t(14;16).

A total of 200 interphase nuclei were analyzed. The cut-off values recommended by the European Myeloma Network (EMN) were used: for deletions and numerical aberrations, the cut-off level was set at 20%; for translocations in the IgH locus as well as other translocations, the cut-off level was set at 10%[9].

2.3. Flow cytometry

Heparinized bone marrow was obtained from patients for the analysis of CD phenotypes. Erythrocyte-lysed whole bone marrow (BM) samples were stained using the following surface four-color combinations (FITC/PE/PerCP or PerCP-Cy-5.5/APC): CD38/CD56/CD19/CD45, CD138/CD28/CD33/CD38, and CD20/CD117/CD138/CD38. These cells were incubated at 4 °C for 30 min and then washed three times with phosphate-buffered saline (PBS) containing bovine serum albumin (BSA). 20,000 events were counted using a flow cytometer (FACS Calibur, Becton Dickinson) and gated by their forward and side-scatter characteristics and CD138 expression. Antigens expression in patients was defined as positive when 20% of the CD138+ population.

2.4. Statistical analysis

The primary end point was the correlation with survival from the time of diagnosis. Progression free survival (PFS) was calculated from the initiation of therapy to the date of death, progression, or the last follow-up. Overall survival (OS) was measured from the initiation of treatment to the date of death or last follow-up, according to the international uniform response criteria [10]. Two-sided Fisher exact tests were used to assess associations between categorical variables, with a confidence coefficient of 95%. The survival curves were plotted using the Kaplan–Meier method, with differences assessed with the log-rank test. The results were considered significant if the p-value was less than or equal to 0.05.

Table 1
Incidence of t(11;14) of each MM type.

Ig type	t(11;14) positive no. (%)
IgA	11/58(19.0)
IgG	25/120(20.8)
Light chain only	9/36(25.0)
IgD	7/12(58.3)
IgM	1/2(50.0)
Nonsecretory	4/9(44.4)
Nonsecretory, IgD, IgM	12/23(52.2)
IgAλ, IgGλ, IgMλ, IgDλ, λlight chain only	29/117(24.8)
IgAκ, IgGκ, IgMκ, IgDκ, κlight chain only	24/111(21.6)

3. Result

3.1. Prevalence of t(11;14) in patients with various plasma cell dyscrasias

In the patients with myeloma, t(11;14) was detected in 60 patients with NDMM (23.7%), and 14 patients with RRMM (18.2%). No statistical difference was detected between NDMM and RRMM ($p = 0.308$). t(11;14) was more common in patients with pPCL (6 of 10 patients) than in those with the NDMM ($p = 0.009$). A high incidence of t(11;14) was also observed in the sPCL patients (5 of 10 patients) than in those with NDMM, but no statistical significance was reached in comparison with the NDMM ($p = 0.059$) because of the limited number of cases. No statistical differences was found between the pPCL and sPCL patients ($p = 1.00$). When pPCL and sPCL were analyzed as a whole, a remarkably higher frequency was observed in the PCL group than in the NDMM group (55.5% versus 23.7%, $p < 0.001$). Five of 60 patients displaying t(11;14) transformed to sPCL, and all patients harbored extra genetic aberrations except for t(11;14) when diagnosed as NDMM.

The incidence of t(11;14) in IgA, IgG, light-chain only, IgD, IgM, nonsecretory NDMM is shown in Table 1. For the cohort as a whole, t(11;14) was observed in 23.7% of all NDMM cases. t(11;14) was observed in 19.0% and 20.8% of IgA and IgG MMs, respectively, whereas it was present in 58.3% of IgD MMs ($p = 0.005$ and $p = 0.004$ for difference with IgA and IgG, respectively). A high incidence of t(11;14) was also detected in nonsecretory MMs (44.4%) and IgM MMs (50.0%), but no statistically significance was reached because of the small number of patients. When the IgD, IgM, and nonsecretory cases were analyzed as a whole, overall t(11;14) was observed in 52.2% of the IgD, IgM, and nonsecretory cases, which was strikingly higher than in IgA and IgG MMs ($p = 0.024$ for IgA, $p = 0.015$ for IgG). There was no significant difference between the incidences of t(11;14) in the light-chain only MM (25%) and in the IgA or IgG MMs ($p = 0.478$ for IgA, $p = 0.595$ for IgG). However, a strong correlation was detected between the t(11;14) and light-chain only isotypes in the primary PCLs, that 5 of 10 primary PCLs displaying the translocation only secreted light chains. No preferential kappa or lambda light-chain gene usage was detected (Table 1).

One study from Fonseca et al. has shown that patients harboring t(11;14) appeared to be very likely to have a serum monoclonal protein of less than 10 g/L [6]. In our study, four of the 60 NDMMs with t(11;14) were nonsecretory MMs, and thus were directly correlated with a reduced secreting capacity. An abnormally high incidence of t(11;14) was also observed in the IgD MMs. All 7 cases of IgD MMs belonged to oligosecretory myelomas with a very low secreting capacity. Next, analysis was restricted to the patients with the classical IgG and IgA MMs. The mean IgA in patients with and without t(11;14) was 45.7 g/L and 47.0 g/L, respectively, and no significant difference was detected compared to the control cohort ($p = 0.896$).