The Impact of Clone Size on the Prognostic Value of Chromosome Aberrations by Fluorescence In Situ Hybridization in Multiple Myeloma

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Abstract

Purpose: Accumulating evidence indicates that intratumor heterogeneity is prevalent in multiple myeloma and that a collection of multiple, genetically distinct subclones are present within the myeloma cell population. It is not clear whether the size of clonal myeloma populations harboring unique cytogenetic abnormalities carry any additional prognostic value.

Experimental Design: We analyzed the prognostic impact of cytogenetic aberrations by fluorescence in situ hybridization at different cutoff values in a cohort of 333 patients with newly diagnosed myeloma and 92 patients with relapsed myeloma.

Results: We found that nearly all IGH-related arrangements were observed in a large majority of the purified plasma cells; however, 13q deletion, 17p deletion, and 1q21 amplification appeared in different percentages within the malignant plasma cell population. Based on the size of subclones carrying these cytogenetic aberrations, the patients were divided into four groups: 0%–10%, 10.5%–20%, 20.5%–50%, and >50%. Receiver-operating characteristics analysis was applied to determine the optimal cutoff value with the greatest differential survival and showed that the most powerful clone sizes were 10% for 13q deletion, 50% for 17p deletion, and 20% for 1q21 gains, which provided the best possible cutoffs for predicting poor outcomes.

Conclusions: Our study indicated that the impact of clone size on prognostic value varies between specific genetic abnormalities. Prognostic value was observed for even a subgroup of plasma cells harboring the cytogenetic aberration of 13q deletion and 1q21 gains; however, 17p deletion displayed the most powerful cutoff for predicting survival only if the predominant clones harbored the abnormality. Clin Cancer Res; 21(9); 2148–56. ©2015 AACR.

Introduction

Recent studies have indicated that intraclonal heterogeneity is a common characteristic of multiple myeloma, and mixed subclones possessing different genomic alterations coexist (1). The clinical characteristics of multiple myeloma are mainly determined by the dominant clones; however, mutations often existed in subclonal populations, as revealed by massively parallel sequencing (2). Moreover, minor clones have been reported to be a reservoir for relapse (3). Selective outgrowth of subclones that have a phenotypic advantage within a given tumor-microenvironmental context can result in fluctuations in subclonal architecture, and these clones later may become dominant even before the initiation of relapse treatment (4).

Multiple myeloma is a heterogeneous disease with the major subtypes defined by the clonal plasma cells with various genetic and epigenetic aberrations (5). Interphase FISH has emerged as the most useful clinical test for genetic aberration detection. However, the determination of cutoff selection remains a matter of debate. Although the European Myeloma Network (EMN) has recommended relatively conservative cutoff values, so far no uniform global cutoffs have been applied, and the cutoffs used in different centers are relatively inconsistent (6). For example, 17p13 deletion was prognostic only if present in at least 60% of the plasma cells in a report from Intergroupe Francophone du Myelome (IFM; ref. 7). However, in studies from Neben and colleagues, 17p13 deletion remained the most important genetic prognostic factor in multiple myeloma if it presents in 10% plasma cells (8, 9).

In contrast with leukemia, multiple myeloma may have chromosomal aberrations carried by only a subset of tumor cells, and the cytogenetic heterogeneity of individual cases reflects the coexistence of cytogenetically defined aberrant plasma cell clones. The size of clones can be measured in a way by the percentage of cells harboring specific cytogenetic abnormalities detected by FISH. These observations raised the questions: (i) what is the
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Translational Relevance
In contrast with leukemia, multiple myeloma may have chromosomal aberrations carried by only a subset of tumor cells. The cytogenetic heterogeneity of individual cases reflects the coexistence of cytogenetically defined aberrant plasma cell clones. It remains a matter of debate what is the prognostic significance of the size of the subclones that harbor a genetic marker, and the cutoffs used in different centers are relatively confusing. Our study indicated that the impacts of clone size on patient outcome were not equal among all forms of genetic abnormalities. Prognostic value was observed for even a subgroup of tumor plasma cells harboring the cytogenetic aberration of 13q deletion and IgH gain; however, 17p deletion displayed the most powerful cutoff for predicting survival only if the major clones carrying the abnormality. Our results highlighted the importance of a cytogenetic abnormality as well as the size of the subpopulation affected.

Materials and Methods
Study design
The myeloma patients included were from a prospective, non-randomized clinical trial (BDH 2008/02; ref. 10). The trial was done in accordance with the Declaration of Helsinki (Version 1996) and approved by the local ethics committees of institutions. We used criteria for symptomatic myeloma as defined by the International Myeloma Working Group (11). The responses were also evaluated using the International Myeloma Working Group criteria (12). A cohort of 333 consecutive patients were enrolled between January 2004 and December 2012, with a median follow-up time of 41 months from diagnosis.

According to their request, patients were assigned to either the thalidomide-based (arm A) or bortezomib-based (arm B) treatment. Arm A consisted of 4 cycles of induction treatment with TAD (thalidomide adriamycin, dexamethasone) or TCD (thalidomide, cyclophosphamide, dexamethasone); arm B consisted of 4 cycles of induction treatment with BCD (bortezomib, cyclophosphamide, dexamethasone) or PAD (bortezomib, adriamycin, dexamethasone). After at least 4 cycles of treatment with partial remission or better response, patients underwent consolidation therapy, which was either autologous stem cell transplant (ASCT) or chemotherapy with the patient’s original regimen according to their request. Subsequently, patients were treated with thalidomide (100–150 mg/day) for 1 year to maintain the response.

When relapse or progression was observed, patients would receive salvage regimen from opposite arm, as well as supportive treatment with zoledronic acid every 1 to 2 months and erythropoetin or granulocyte colony-stimulating factor. All patients underwent prophylactic acyclovir treatment.

FISH studies
As previously reported, all multiple myeloma cell samples were purified using the Millenyi technology (anti-CD138–coated magnetic beads) before FISH, enabling a plasma cell purity higher than 90% (13). Plasma cells were then analyzed using DNA probes (Abbott Molecular) specific for the following chromosomal aberrations: 13q14 deletion, 17p13 deletion, t(11;14), t(4;14), and t(14;16). Gains of 1q21 were assessed using a bacterial artificial chromosome probe at 1q21 (RP11-307C12; ref. 14). A total of 200 interphase nuclei were analyzed.

Statistical analysis
The primary endpoint was the correlation of cytogenetic abnormalities 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 (15). 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.

ROC analysis was applied to determine the optimal cutoff value that yielded the greatest differential in survival. We used Youden index to assess the optimum cutoff point for cytogenetic abnormalities by FISH (16). The cutoff value that best discriminated (in mean of sensitivity and specificity) between survival and death was used for OS, and the cutoff value that best discriminated between progression and no progression was used for PFS.

Results
Frequencies and patterns of cytogenetic alterations
The hybridization efficiency was assessed on interphase nuclei obtained from the bone marrow (BM) of healthy donors. BM samples from 20 normal individuals were used to establish cutoff values. "Means±3×SD" of the percentages of nuclei with abnormal signals were calculated as the cutoff values for each probe. At least 200 nuclei were evaluated for each probe. The threshold levels were as follows: 13q14 deletion, 5.98%; 17p13 deletion, 3.98%; 1q21 gains, 2.15%; IgH rearrangement, 4.16%; t(11;14), 2.24%; t(4;14), 3.18%; and t(14;16), 2.76%.

By definition, an abnormality was diagnosed only when the percentage of cells with aberrant FISH signals was greater than the cutoff values. However, to avoid false positives, cutoff values recommended by the EMN were used: for deletions and numerical aberrations, the cutoff level was set at 20%; and for translocations in the IgH locus as well as other translocations, the cutoff level was set at 10% (17). Because the small number of purified plasma cells in some specimens and the failure of FISH in some cases, we were unable to test the full set of probes in all patients. The exact number of probes tested and the frequency of cytogenetic abnormalities in newly diagnosed and relapsed multiple
myeloma are shown in Table 1. According to the percentage of plasma cells involved, patients with cytogenetic aberrations were divided into four groups: 0%–10%, 10.5%–20%, 20.5%–50%, and >50%. The distributions of each probe is shown in Table 2. The frequency of malignant plasma cells in which a deletion of 13q14 was detected varied between 20% and 100% in newly diagnosed multiple myeloma, as was true for 17p13 deletion and 1q21 gains. Although IgH rearrangement was also detected varying between 20% and 100%, nearly all patients with t(11;14), t(4;14), or t(14;16) had more than 50% of plasma cells with these abnormalities (Supplementary Table S1). Our results also demonstrated that the incidence of IgH1 gains, 17p deletion, and t(14;16) was higher in relapsed multiple myeloma than in newly diagnosed multiple myeloma; however, the frequency of 13q deletion and IgH translocation were comparable between the two groups (Table 1). The molecular events leading to the generation of myeloma progenitor cells are predicted to be present in all clones, whereas secondary alterations during disease progression are expected to occur in subclonal fractions. These findings support the assumption that acquisition of a chromosomal translocation into the Ig loci is a founder genetic event, whereas 17p13 deletion and 1q21 gains typically correspond to a secondary genetic change. Therefore, we focused on the cutoff selection of 13q14 deletion, 17p13 deletion, and 1q21 gains.

Impact of 17p13 deletion on survival at different clone sizes
Chromosome 17p13 deletion was observed in 6.6% (22 of 333) patients by EMN cutoff criteria. In the current study, the median percentage of plasma cells harboring 17p13 deletion was 64.5% (range, 24.5%–100%). According to the percentage of plasma cells involved, patients with 17p13 deletion were divided into four groups: 0%–10%, 10.5%–20%, 20.5%–50%, and >50%. The median PFS was 24.0 (95% CI, 21.2–26.8), not reached, 20.0 (95% CI, 17.0–23.0), and 4.0 months (95% CI, 0.0–11.5), respectively (P < 0.001; Fig. 1). Therefore, patients with 17p deletion were divided into two groups using 50% as cutoff: the median PFS of which was 4.0 (95% CI, 0–12.2) and 24.0 months (95% CI, 20.9–27.1), respectively (P < 0.001), whereas the median OS was 16.0 (95% CI, 6.7–25.3) and 40.0 months (95% CI, 26.2–53.9), respectively (P < 0.001).

Impact of 1q21 gains on survival at different clone sizes
Chromosome 1q21 gains were observed in 49.2% (157 of 319) patients by EMN criteria. In the current study, the median percentage of plasma cells exhibiting 1q21 gains was 75.5% (range, 20.5%–100%). According to the percentage of plasma cells involved, patients with 1q21 gains were divided into four groups: 0%–10%, 10.5%–20%, 20.5%–50%, and >50%. The median PFS was 31.0 (95% CI, 23.9–38.0), 46.0 (95% CI, 3.4–88.6), 11.0 (95% CI, 2.2–19.8), and 14.0 months (95% CI, 9.6–18.3), respectively; and the median OS was 53.0 (95% CI, 38.6–67.3), not reached, 17.0 (95% CI, 7.9–26.1), and 24.0 months (95% CI, 20.1–27.9), respectively for these four subgroups.

Cutoff points of 20% and 25% gave the highest, but similar Youden values to progression; cutoff points of 12.7% and 22.5% gave the highest, but similar Youden values to death (Supplementary Fig. S1). We used 20.0% to group patients into two categories: the median PFS was 11.0 (95% CI, 9.9–12.1) and 23.0 months (95% CI, 19.2–26.8), respectively (P < 0.001); and the median OS was 21.5 (95% CI, 17.5–25.5) and 52.5 months (95% CI, 29.3–75.7), respectively (P < 0.001; Fig. 2).

Impact of 13q14 deletion on survival at different clone sizes
Chromosome 13q14 deletion was detected in 47.4% (158 of 333) patients by EMN criteria. The median percentage of plasma cells involved, patients with 13q14 deletion were divided into four groups: 0%–10%, 10.5%–20%, 20.5%–50%, and >50%. The median PFS was 26.8 (95% CI, 2.2–19.8), respectively (P < 0.001), whereas the median OS was 38.0 (95% CI, 8.0–67.3), not reached, 12.2 (95% CI, 7.9–26.1), and 16.0 months (95% CI, 6.7–25.3), respectively (P < 0.001; Fig. 1).
According to the percentage of plasma cells involved, patients with 13q14 deletion were divided into four groups: 0%–10%, 10%–20%, 20%–50%, and >50%; Their median PFS was 33.5 (95% CI, 24.3–42.7), 8.0 (95% CI, 0–18.3), 21.0 (95% CI, 6.1–35.9), and 16.0 months (95% CI, 12.9–19.0), respectively; whereas the median OS was 55.5 (95% CI, 36.8–74.2), 9.0 (95% CI, 0–21.8), 35.0 (95% CI, 18.9–51.1), and 26.0 months (95% CI, 20.9–31.1), respectively for these four subgroups.

To screen for patients likely to progress or die of multiple myeloma based on 13q14, we chose a cutoff point for 13q14 deletion that gave the highest possible Youden index. A cutoff point of 10% gave the highest Youden value for both progression and death (Supplementary Fig. S1). The median PFS was 17.0 (95% CI, 13.8–20.2) and 33.5 months (95% CI, 24.3–42.7), respectively (P < 0.001), and the median OS was 25.0 (95% CI, 20.1–29.9) and 55.0 months (95% CI, 36.8–74.2), respectively (P < 0.001; Fig. 3).

In practice, there was considerable concern that results just above the actual mean ± 3SD were artifactual, and 10% cutoff may not reflect the reality. We analyzed the patients only having 25% or more abnormal cells. We divided the patients into three groups: 0%–25%, 25%–50%, and >50%. We found that patients with del(13q) >50% have the shortest PFS. However, regarding OS, patients with del(13q) <25% have the longest OS, and there are no differences between 25%–50% and >50% groups. Therefore, when analysis was restricted to patients having 25% or more abnormal cells, 25% is the proper cutoff value.

It is well known that the cytogenetics of myeloma are not randomly distributed, and 13q deletion is usually associated with other high-risk cytogenetic aberration, such as 17p deletion or t(4;14). We analyzed the prognostic value of del(13q) only [without t(4;14) or 17p deletion]. We used three cutoff value: 10%, 20%, and 50%. We found that it has a slight impact on OS using 10% as cutoff value. It has no impact on PFS and OS using cutoff of 20% and 50%. It seems that the prognostic value of del(13) was almost entirely dependent on the frequent association with t(4;14) and del(17p).

Multivariate analysis

We then performed a multivariate analysis on all the chromosomal aberrations significantly associated with PFS and OS in the univariate analysis, as well as other parameters associated with survival in this series. Of these, three parameters were statistically independent predictors of PFS: chromosomal aberration 17p deletion in more than 50% plasma cells [HR, 2.455 (95% CI, 1.818–3.315), P < 0.001], 1q21 gains in more than 20% plasma cells [HR 2.401 (95% CI, 1.695–3.399), P < 0.001], and advanced
ISS stage [HR, 1.377 (95% CI, 1.082–1.751), \(P = 0.009\)]. A similar analysis also identified the parameters del(17p) [HR, 1.754 (95% CI, 1.291–2.383), \(P < 0.001\)], 1q21 gains [HR 1.974 (95% CI, 1.303–2.992), \(P < 0.001\)], and advanced ISS stage [HR 1.546 (95% CI, 1.142–2.093), \(P = 0.005\)] as independent predictors for prediction of OS.

**Discussion**

The results of our study showed that there were significant differences among the sizes of clones possessing different cytogenetic aberration. Nearly all IgH-related arrangements were detected in at least 50% of purified plasma cells. However, 13q deletion, 17p deletion, and 1q21 amplification may appear in different percentages within the malignant plasma cell population of a given multiple myeloma patient. The optimal clone size of 13q deletion, 17p deletion, and 1q21 amplification for prognostic value were 10%, 50%, and 20% respectively in our center. Multiple myeloma develops as a result of multistep tumorigenic events characterized by frequent and complex genomic abnormalities that essentially contribute to the pathogenesis of this disease. Each step of this sequel is driven by an additional genetic event. At the top hierarchical level, cytogenetic abnormalities can be divided into primary and secondary genetic lesions. Primary genetic events occur early in the pathogenesis of multiple myeloma, whereas secondary genomic changes are acquired with disease progression from monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma and finally secondary plasma cell leukemia. By using FISH, a primary event should be detectable in nearly 100% of purified or selected plasma cells and are unlikely to change dramatically during tumor progression. However, secondary changes may only present in subpopulations and can appear with increasing frequency throughout accumulation of malignant plasma cells. These progression-related aberrations appear with a certain probability and are thus more frequent in relapsed myeloma.

Our results demonstrated that the frequency of 17p deletion and 1q21 gains was much higher in relapsed multiple myeloma, but no significant differences was seen in 13q deletion and IgH translocations. The incidence of t(4;14) was also higher in relapsed multiple myeloma, because patients displaying t(4;14) were at a high risk of relapse. Moreover, the frequency of malignant plasma cells in which a 17p deletion or 1q21 gains can be detected varied between 20% and 100% in newly diagnosed multiple myeloma. Although IgH rearrangement varied between 20% and 100%, nearly all patients with t(11;14), t(4;14), or t(14;16) had more than 50% of plasma cells with this abnormality. IgH rearrangement was detected using IGH dual color,
break-apart rearrangement probe, and sometimes it is difficult to judge the result by assessing the separation of probe signals. T(11;14), t(4;14), and t(14;16) were detected using dual color, dual fusion translocation probe, allowing for objective judgment of the result. This may explain the discordance of frequency between IgH arrangement and T(11;14), t(4;14), or t(14;16).

Our results suggested that 17p deletion and 1q21 gains were classic secondary cytogenetic abnormalities, and that IgH-related translocations were the initiating events in multiple myeloma pathogenesis. However, we were unable to judge whether 13q deletion was a primary or secondary cytogenetic aberration. Whereas some studies reported a similar prevalence in MGUS, indicating that 13q deletion is an initial event in the disease, subsequent publications showed a slightly lower prevalence, indicating that it may also be a progression event in some cases (18, 19). Our results indicated that the clone size analysis was critical for 13q14 deletion, 17p13 deletion, and 1q21 gains; however, IgH-related translocations such as t(11;14), t(4;14), and t(14;16) usually appeared in the majority of myeloma cells, and their cutoffs were proven not critical for the analysis. We thus focused the subsequent analysis on 13q14 deletion, 17p13 deletion, and 1q21 gains.

FISH is an indispensable method to detect cytogenetic aberrations. Laboratories prefer to use their own in-house established mean±3SD from normal BM controls as cutoff value, however, normal plasma cells represent only 0.25% of BM mononuclear cells, and these cutoff values are mainly from other cellular elements of the BM instead of plasma cells. From our experience and that of other laboratories, fluorescent signals are generally of lower intensity in the clonal PCs compared with other cellular elements of the BM (20). The decreased hybridization efficiency may result from the poor DNA accessibility for FISH probes due to abundant immunoglobulin (21). These discrepancies raise the question regarding setting accurate cutoffs in FISH experiments, especially in studies searching for deletions. How conservative the cutoffs should be remains a matter of debate, and the cutoff values are not exactly comparable among different centers. As shown in Table 3, the cutoff values are different between Arkansas, Mayo Clinic, Toronto General Hospital, IFM, University of Heidelberg, and Chinese centers.

Among all multiple myeloma genetic factors, deletions of 17p remain the single most important prognostic factor, present in approximately 10% of cases at the time of diagnosis (13, 22). Deletions of 17p13 confer an inferior outcome for patients irrespective of the treatment modality used (23, 24), but the optimal cutoff remains unknown. For example, patients harboring 10% to 20% cells positive for 17p13 deletion are considered high-risk in Canada (25, 26) and standard risk in the Arkansas group (14, 27), using different cutoff values. The present study
divided the patients with 1q21 deletion into four groups according to the percentage of plasma cells involved. Not surprisingly, patients harboring 17p13 deletion in >50% malignant plasma cells had the worst outcome. ROC methodology is routinely used to check the utility of a diagnostic marker and the best cutoff value of prognostic factors (28). Although cutoff points of 4.5% and 6.5% gave the highest Youden values to progression and death, respectively, in practice there was considerable concern that results just above the actual mean ± 3 SD may not be meaningful. From the Kaplan–Meier curve, we also found that patients with 17p deletion in >50% malignant plasma cells had the shortest OS, whereas the other three curves were not distinctly separated. In accordance with the studies of Avet-Loiseau and Neben and colleagues (7, 8), the most powerful 17p13 deletion cutoffs for predicting PFS and OS were 50%. A growing body of evidence indicates that small clones harboring 17p deletion are already present at the onset, and that selection pressure and clonal evolution cause their progressive dominance over time (29). Moreover, obligate haploinsufficiency is thought to be the mechanism underlying 17p deletion-induced tumorigenesis (30). These data may explain why the powerful prognostic value is only when 17p deletion involved the majority of the plasma cells. However, as the incidence of 17p deletion was low (<10%), and the number of patients with 17p deletion in each group was limited, this result should be validated in larger cohorts of patients.

Multiple studies have shown that chromosome 1q21 gains are associated with an inferior outcome in multiple myeloma (9, 10, 31), which has been supported by several basic researches (32, 33). As in previous studies, we found that the percentage of myeloma cells carrying a 1q21 gains within total myeloma cells of a given patient increased with disease progression, indicating that 1q21 was a “progression-related” aberration. This study divided the patients with 1q21 gains into four groups according to the percentage of plasma cells involved. Based on the survival curve, patients were divided into two groups with disparate PFS and OS by a cutoff value of 20%. Moreover, the cutoff point of 20% gave the highest Youden values. Therefore, 20% may be the proper cutoff value for 1q21 gains.

Deletion of chromosome 13 is one of the most common abnormalities, found in about 50% of newly diagnosed multiple myeloma patients by FISH analysis. In our study, the frequency of 13q deletion was comparable between newly diagnosed and relapsed multiple myeloma. It seemed that 13q14 deletion was a primary cytogenetic aberration, but the percentage of plasma cells exhibiting del(13) varied in a wide range. There is still no consensus whether 13q deletion is a primary or secondary cytogenetic aberration. Although a cutoff point of 10% gave the highest Youden value to both progression and death, 13q14 deletion was not found to be an independent prognostic factor in the multivariate analysis, irrespective of the cutoff chosen. Actually, most of the prognostic power of 13q14 deletion was related to 17p13 deletion and 1q21 gains, which are frequently associated with 13q14 deletion.

We divided the patients with 13q deletion into four groups according to the percentage of plasma cells involved. Unexpectedly, patients with 13q14 deletion in 10% to 20% of their plasma cells had the shortest OS; the OS of patients with 13q deletion in 20%–50% and >50% of their plasma cells was comparable. Recent clinical and biologic data are consistent with the notion that intraclonal heterogeneity is a common characteristic of multiple myeloma. If a chromosomal aberration appears in >70% of myeloma cells, but another in only a smaller percentage of the same population (20%), there is the presence of a so-called subclonal aberration (34). Patients with 13q deletion in 10% to 20% of their plasma cells may possess more subclones, if other cytogenetic aberrations exist at the same time. Therefore, it is more
useful to perform a panel of cytogenetics, rather than a single factor.

Taken together, our data demonstrated that, in contrast with primary IgH translocations, there is variability in the size of the abnormal clones carrying 17p deletion, 13q deletion, and 1q21 gains. The impacts of clone size on patient outcome were not equal among all forms of genetic abnormalities. In our center, the 50%, 20%, and 10% were the optimal cutoff points for 17p deletion, 1q21 amplification, and 13q deletion, respectively, in terms of prognostic value in this study. The prognosis was affected even by a subgroup of tumor plasma cells harboring the cytogenic aberration of 13q deletion and 1q21 gains; however, for 17p deletion, the most powerful cutoff for predicting survival existed only when the clones become dominant. Our results highlighted the importance of a cytogenetic abnormality as well as the size of the subpopulation affected.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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