Cancer Genetics 209 (2016) 423–429

Cancer Genetics

ORIGINAL ARTICLE

Monosomal karyotype of chromosome 5/7 was an independent poor prognostic factor for Chinese myelodysplastic syndrome patients

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Monosomal karyotype (MK) was defined as the presence of at least 2 autosomal monosomies or of a single monosomy associated with at least one additional structural abnormality. 6.4–16.3% myelodysplastic syndrome (MDS) patients were reported to fulfill the criteria for MK and associated with poor prognosis in the majority of patients with MDS. In order to further clarify the prognostic significance of MK in Chinese MDS patients, 2080 primary patients were retrospectively analyzed in our center. MK was observed in 8.1% patients (168/2080), and monosomies of chromosome 5/7 were the most frequent types of MK. We further found that MK was significantly associated with elderly patients, higher bone marrow blasts and relatively poor cytogenetics. In addition, MDS patients with MK (n = 59) had poor survival than those without MK (n = 491) in total cohort ($P < 0.001$), and there was significant difference in the OS between the patients with MK (n = 56) and without MK (n = 53) in the relatively poor cytogenetics group ($P = 0.0025$). Incorporation of MK into IPSS-R could further stratify MDS patients into different prognostic groups ($P < 0.001$). Interestingly, monosomies of chromosome 5/7 rather than MK were significantly related to shorter OS (HR = 2.709, $P < 0.001$) by multivariate analysis. In conclusion, our results suggested that 8.1% MDS patients were presented with MK, and the incidence of MK increased with the number of cytogenetic abnormalities. Monosomies of chromosome 5/7 were the most frequent MK as well as an independent poor risk factor for OS in Chinese MDS patients.

Keywords Myelodysplastic syndrome (MDS), monosomal karyotype (MK), monosomies of chromosome 5/7, prognostic significance

Introduction

Myelodysplastic syndromes (MDS) are heterogeneous clonal hematopoietic neoplasms, associated with peripheral cytopenias and the risk of transformation into acute myeloid leukemia (AML) (1). Cytogenetic abnormalities occur in roughly half of the patients with MDS, which have been regarded as the most important prognostic factor in MDS patients (2). In 2012, the revised International Prognostic Scoring System (IPSS-R) defined 5 cytogenetic-risk groups with different clinical outcomes, which was able to guide the diagnosis and therapy of MDS in clinical practice (3,4).

Monosomal karyotype (MK) was first introduced by Breems et al. in AML patients, and it was be defined as the presence of at least 2 autosomal monosomies or of a single monosomy associated with at least one additional structural abnormality (5). It was reported that 11–13% of AML patients were indentified with MK, which was presented more frequently in older patients, also had significantly lower complete remission (CR) rate and shorter OS (5,6). It was reported that 6.4–16.3% of MDS patients presented with MK and these patients likely had poor survival even after allogeneic

Received March 16, 2016; received in revised form June 2, 2016; accepted June 14, 2016.

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2210-7762/$ - see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cancergen.2016.06.007

hematopoietic stem cell transplantation (HSCT) (7–11). Additionally, monosomies of chromosomes 5 and/or 7 were the most frequent types of MK and independently associated with lower OS (7). However, considering hitherto there were few reports on Chinese MK MDS patients and the prognosis of MK was not well verified in a well-designed clinical trial, we retrospectively analyzed a large cohort of MDS patients from a single center in China, and further explored the frequency, clinical characteristics and prognostic significance of MK in MDS patients.

Patients and methods

Patients and therapy

2080 patients diagnosed with primary MDS were retrospectively analyzed from January 1984 to December 2013 at our center. The diagnosis and classification of MDS were based on the French–American–British (FAB) and 2008 World Health Organization (WHO) criteria. In total cohort, only 550 patients provided the complete follow-up data, and the median follow-up time was 18 months (range, 1–144 months).

Therapy strategies: during their disease course, 442 (80.4%) MDS patients with lower risk received supportive care alone. 108 (19.6%) MDS patients with higher risk (intermediate and high risk group) received disease-modifying therapy as following: 54 patients received only chemotherapy with (n = 29) or without (n = 25) decitabine, while 54 patients received allogeneic hematopoietic stem cell transplantation. Among 54 patients who undergone allo-HSCT treatment, MK was only identified in 2 (2/54, 3.7%) HSCT patients.

Cytogenetic analysis

Chromosome preparations were performed on bone marrow samples using the standard procedures of conventional R-banding technique. Final karyotypic results were described according to the International System for Human Cytogenetic Nomenclature 2009. Complex karyotype (CK) was identified as the presence of 3 or more independent abnormalities. MK was defined as the presence of at least 2 autosomal monosomies or of a single monosomy associated with at least one additional structural abnormality. Monosomies of the sex chromosomes were not considered sufficient to meet the definition of MK.

Statistical analysis

Statistical analyses were performed using the software SPSS 23.0 and Graph Pad Prism 6. Differences in categorical variables were calculated using a chi-square test and differences in continuous variables by means of the Mann–Whitney U-test. Survival probabilities were estimated by the Kaplan–Meier method. Factors affecting overall survival (OS) were analyzed using the Log-Rank test in univariate analyses and the Cox proportional hazards model in multivariate analyses. For all analyses, P values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Monosomies of chromosome 7/5 were the most frequent types of MK

A total of 2080 patients, 1260 males and 820 females, were included in the study. The median age was 51 years (range, 2–89 years). CK was identified in 277 patients (277/2080, 13.3%). MK was observed in 168 patients (168/2080, 8.1%), of whom 156 (156/168, 92.9%) had CK. In 168 MK patients, all chromosomes (except chromosome 1) were involved in at least one monosomy. Notably, the frequencies of autosomal monosomies in the MK patients were as following: chromosomes 7 and 5 (n = 56), chromosome 18 (n = 36), chromosome 17 (n = 32), chromosome 12 (n = 22) and chromosome 13 (n = 20) (Table 1).

Clinical characteristics of MK$^+$ patients with MDS

550 patients with primary MDS who had available follow-up data were collected. The median age at diagnosis was 57 years (range, 12–89), and there were 234 patients (234/550, 42.5%) older than 60 years. MK was found in 59 patients (59/550, 10.7 %), of whom 53 (53/59, 89.8%) had CK. 56 MK (56/59, 94.9%) patients were assigned to poor- and very poor-cytogenetic groups by IPSS-R, while 57 MK (57/59, 96.6%) patients were assigned to poor and very poor IPSS-R risk groups. MK was dramatically associated with older age (median

Table 1 Frequencies of chromosomes involved in monosomies

Chromosome in monosomy	Frequency	Isolated	Combined
1	0	0	0
2	7	2	5
3	17	3	14
4	8	1	7
5	56	8	48
6	11	3	8
7	56	12	44
8	13	1	12
9	9	3	6
10	8	1	7
11	15	6	9
12	22	2	10
13	20	1	19
14	11	1	10
15	17	1	16
16	16	0	16
17	32	5	27
18	36	7	29
19	19	2	17
20	18	4	14
21	19	2	17
22	15	1	14

Isolated: patients with 1 monosomy and at least 1 additional structural abnormality; Combined: patients with 2 or more autosomal monosomies.