Trisomy 8 is Associated with Favorable Outcome in the Patients with Myelodysplastic Syndromes Treated with Allogeneic Hematopoietic Stem Cell Transplantation

Nikolay N. Mamaev, Maria V. Latypova, Tatiana L. Gindina, Mikhail M. Kanunnikov, Anna A. Osipova, Sergey N. Bondarenko, Sergey S. Riumin and Liudmila S. Zubarovskaya

RM Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantology, Pavlov University, St. Petersburg, Russia

Abstracts: Favorable prognostic significance of sole trisomy 8 and its associations with additional chromosome aberrations was confirmed in 7 adult and 3 pediatric patients with myelodysplastic syndromes treated with hematopoietic stem cell transplantation (HSCT). The group of comparison included 10 MDS patients with sole monosomy 7 or 5 chromosome and those within complex karyotypes (CK). Cytogenetic investigations were carried out according to standard GTG and multi-colored fluorescence *in situ* hybridization (mFISH) techniques. Our data revealed significant difference in overall survival (OS) between the tested and control groups (p=0.045) thus being additional argument reinforcing the concept of favorable prognosis of trisomy 8 in HSCT-treated MDS patients. Eight of ten patients (5 with sole trisomy 8 and three with more complex karyotypes) are alive. Of the deceased patients, one had CK trisomy 8 was associated with poor-prognostic monosomy 7. In accordance with experimental findings Sloand *et al*., 2007, this favorable effect of trisomy 8 in MDS patients might be linked with inhibition of programmed cell death with anti-apoptotic proteins, including myc, which are activated in these cases and needs additional in-depth studies.

Keywords: Myelodysplastic syndromes, Trisomy 8, Anti-apoptotic proteins, Hematopoietic stem cell transplantation, Favorable outcome.

INTRODUCTION

An important role of cytogenetic aberrations at diagnosis and prognosis assay in some oncohematological disorders is evident. Meanwhile there are interesting data concerning favorable role of trisomy 8 in patients with myelodysplastic syndromes (MDS) [1, 2], who were treated with alloHSCT. In order to test this concept we have recently studied the results of alloHSCT in a relatively small cohort of MDS patients with sole trisomy 8 and its combinations with other chromosome aberrations too.

MATERIAL AND METHODS

This tested group consists of 7 adult and 3 pediatric patients (6 females. 4 males) aged from 4 till 51 years (mean=26.2 years). All patients were treated by means of allogeneic hematopoietic stem cell transplantation (alloHSCT), either from unrelated matched donors (n=7), or from 2 related and 1 haplo-HSCTs. The chosen conditioning regimens were myeloablative (MAC), or of reduced toxicity (RIC) in 7 and 3 patients, respectively. Overall survival (OS) was estimated from the time of alloHSCT. For karyotype assay were used: 1) standard GTG technique; and 2) multicolored fluorescent in situ hybridization approach (mFISH) which were published by us earlier in details [2, 3]. Statistical evaluation of OS was carried out by means of Kaplan-Meyer method.

RESULTS

The basic clinical and cytogenetic data, presented at the Tables **1** and **2** show presence of sole trisomy 8 found in 6 tested patients. In 4 other cases, it was associated with additional chromosome aberrations. Of note, malignant cells in two patients (#4 and 8) contained very complex karyotypes (CK) (Figure **1**). As a result, OS ranged from 3411 to 78 days (a mean of 1364 days). It should be mentioned, that 8 of these patients are alive up to this day. Among them are 5 patients (#1-3, 6, 9) with sole trisomy 8, and 3 patients whose karyotypes were complicated with other chromosomal abnormalities. The most complex karyotype was revealed in the young female whose case has been recently published by us [3]. Longer OS (3411-1636 days) was characteristic for 3 patients (#1-3) with sole trisomy 8, being shorter (1440-1068 days) in 3 patients with more complex karyotypes (#4, 5, 7) and 1 pediatric patient with sole trisomy 8 who was treated with haplo-HSCT. The shortest OS was registered in 1 patient with sole trisomy 8 (#10) which it

*Address correspondence to this author at the RM Gorbacheva Research Institute of Pediatric Oncology, Hematology and Transplantology, Pavlov University, St. Petersburg, Russia; Tel. Office: +7(812)3386265;
E-mail: nikmamaev524@gmail.com

Table 1: Results of Hematopoietic Stem Cell Transplantation in MDS Patients with Sole Trisomy 8 or its Combination with other Chromosome Abnormalities

Patient		Type of MDS	IPSS-R	Karyotype	Hematopoietic Stem Cell Transplantation		OS (days)
№	Age (years), gender				Type	CR	
1	48,f	RS	intermed	47,XX,+8[10]/46,XX[6]	unrelated	RIC	3411+
2	18, f	EB1	low	47,XX,+8[15]	unrelated	MAC	1939+
3	27, m	EB2	high	47,XY,+8[4]/46,XY[16]	unrelated	MAC	1636+
4	22, f	EB2	very high	ish.45,XX,t(1;12)(p36;p13),der(2)t(2;11)(q35;?),der(4)t(7;8;4),der(5)t(5;8)(q13;q22),-7,der(8)t(8;7;8;4)x2, der(8)t(8;7;8;7;8;4), der(8)t(5;8), der(8)t(12;8;7), der(13)t(13;8;12)[cp10][24XCyte]	unrelated	RIC	1440+
5	23, f	MLD	very high	48,XX,t(1;19)(q23;q13),+8, +der(19) t(1;19)[4] /96, idem,x2[1]/46,XX[15]	Haplo	MAC	1163+
6	4, m	EB1	-	47,XY,+8[11]/46,XY[9],	haplo	MAC	1161+
7	11, m	U	-	47,XY,ins(1;?)(q21;?),+8[20]	related	RIC	1068+
8	40, f	EB2	low	ish.47,XX,der(1)t(1;13), der(3)t(1;3)(?;p21),der(5)del(5)(p11)del(5)(q11),der(7)del(7)(p?)del(7)(q?), +8, der(13)t(5;13) (?;q12), der(14)t(3;14)(?;q?), der(17)t(5;17)(?;p11)[24XCyte]	unrelated	MAC	886*
9	18, m	MLD	very high	47,XY,+8[15]	unrelated	MAC	861+
10	51, f	EB2	high	47,XX,+8[7]/46,XX[13]	related	MAC	78*

Notes: EB1, EB2 and RS: MDS with excess blasts of 1 and 2 grade, RS, MDS with ring sideroblasts; Intermed, intermediate; CR,-conditioning regimen; MAC and RIC, myeloablative and reduced- toxicity CR; haplo, haploidentical transplantation; OS, overall survival; Symbols + and * in the OS graph show surviving and deceased patients, respectively.

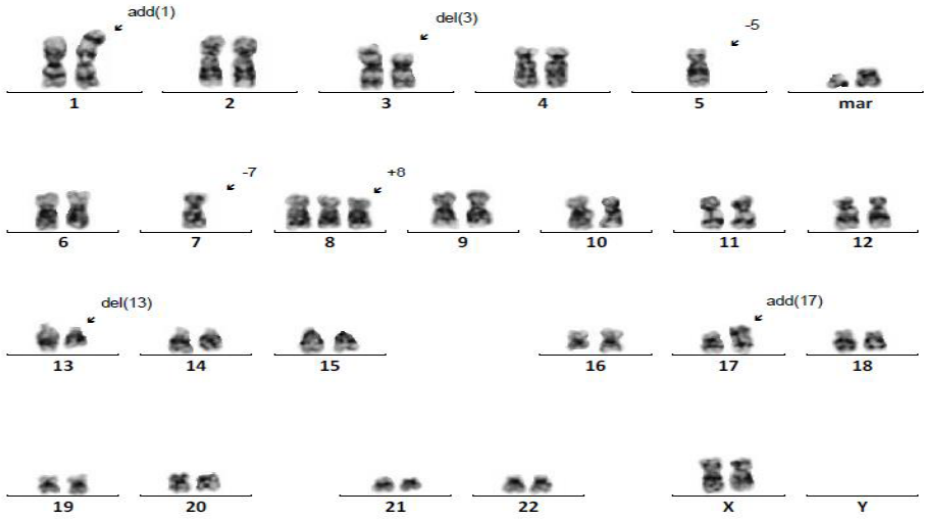
Table 2: Results of HSCT in Mixed Group of Adult and Pediatric MDS Patients with sole Monosomy 7 or 5, and their Combinations within Complex Karyotypes

Patient		Type of MDS	IPSS-R	Karyotype	Hematopoietic Stem Cell Transplantation		OS (days)
№	Age (years), gender				Type	CR	
11	54,f	EB2	Intermed	45,XX,-7[4]/46,XX[16]	related	RIC	1597*
12	22, m	MLD	low	45,XY,-7[9]/46,XY[1]	haplo	MAC	966+
13	14, f	U	high	45,XX,-7[20]	unrelated	MAC	880+
14	54, f	EB2	very high	46,XX,del(5)(q13q33)[2]/46,XX[18]	unrelated	RIC	572+
15	40, f	EB2	very high	45,XX,-7[15]	related	MAC	448+
16	57, m	EB1	-	46,XY,del(5)(q13q33)[19] /46,XY[1]	related	RIC	274*
17	22, m	EB1	-	45,XY,-7[20]	unrelated	RIC	271*
18	58, f	EB2	low	ish.45,XX,dup(1)(q21q32),del(3)(q21q27),der(5)t(5;7)(q13;?), -7, del(12)(p11p12)[24XCyte]	unrelated	RIC	245*
19	43, m	MDS	very high	46,XY,del(5)(q22q35)[20]	unrelated	MAC	200*
20	37, f	EB2	high	ish.46,XX,der(5)t(5;7;5;7),-7, der(12)t(12;13)(p13;q?), del(13)(q11),+r(13)[24XCyte]	unrelated	RIC	164*

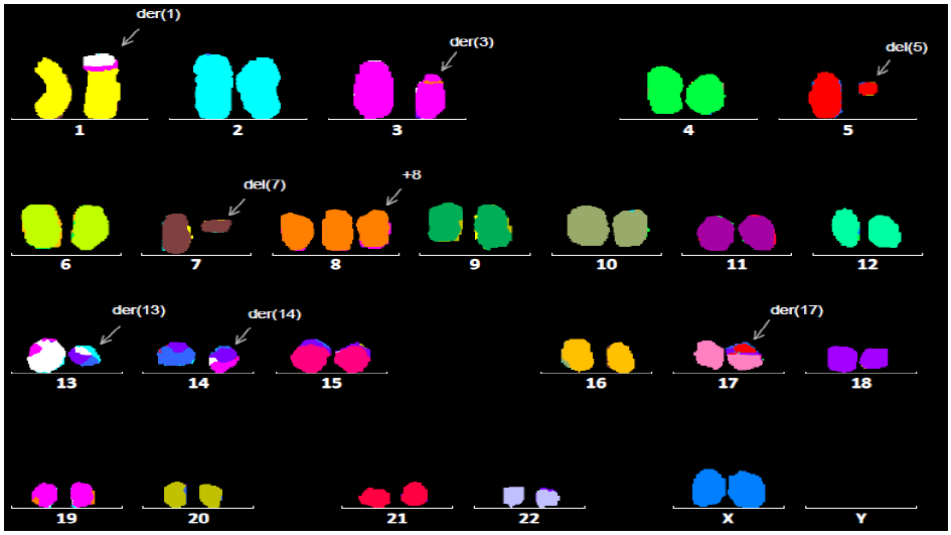
Notes. The same as for Table 1.

might be explained with transplant failure associated with bone marrow fibrosis of high-grade.

Comparative analysis of the patients data the subgroups with trisomy 8 and without this chromosome



A



B

Figure 1: Complex karyotypes of two bone marrow cells from female patient with MDS, in whom final assessment of chromosome aberrations was achieved only by means of both GTG (**A**) and mFISH (**B**) approaches. In sum, the following karyotype was diagnosed: ish.47,XX, der(1) t(1;13)(p3?4;q?), der(3)t(1;3)(?;p21), der(5)del(5)(p11) del(5)(q11), der(7) del(7)(p?)del(7)(q?), +8, der(13)t(5;13)(?;q12), der(14) t(3;14)(?;q?), der(17)t(5;17)(?;p11)[24XCyte].

abnormality showed that the mean age of the patients with trisomy 8 and those free of this abnormality were 26.2 and 40.1, with similar female/male ratio (6/4). The types of HSCT and conditioning regimens did not sufficiently differ as well. Meanwhile, OS rates of the patients with trisomy 8 were longer than those from the group of comparison (Figure **2**; $p<0.045$). The groups also included 10 adult (n=9) and pediatric (n=1) patients (6 female and 4 male) aged 14 -57 years (mean= 40.1 y). In 5 of them, an advanced variant of MDS was diagnosed, whereas stage EB1 was assessed in 2 patients Further on, MDS with multi-lineages dysplasia was diagnosed in one case (#12), whereas in a single pediatric case the type of MDS was not recognized.

DISCUSSION

Our study can support earlier findings of favorable outcome of MDS patients with trisomy 8 treated with alloHSCT [1]. Our data are in accordance with those obtained by Japanese investigators who studied the great cohort of such patients. Therefore, we may suggest that trisomy 8 might be favorable for outcome. In contrast to Japanese cohort, our small group included not only adult patients but pediatric cases as well. Further on, a part of our patients had karyotypes with 3 and more abnormalities which were excluded from the Japanese cohort. Meanwhile, excellent responses onto chemotherapy were obtained by us in some patients with great changes in their karyotypes

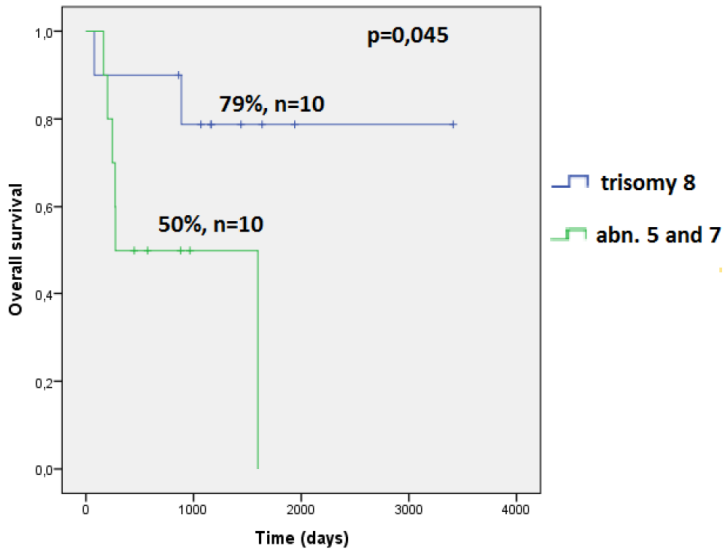


Figure 2: Difference in overall survival of MDS patients with trisomy 8 and abnormalities of chromosome 7 and 5 treated with HSCT.

(for instance, #4), whose GTG- and mFISH-stained karyotypes have been recently presented in details [3]. In our opinion, these unusual data might be explained with increased production of antiapoptotic proteins, including myc, which has been shown experimentally [4], and need further in-depth investigations.

Since ineffective hematopoiesis is closely linked to cellular apoptosis being considered a crucial factor of MDS pathogenesis, the presented data concerning favorable outcome in MDS patients with trisomy 8 treated with HSCT may be relevant for both theory and practice and need further in-depth studies.

CONFLICT OF INTERESTS

There are no any conflict

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Address all correspondence to: nikmamaev524@gmail.com

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