Chapter 4

Chromosome Abnormalities and Hematopoietic Stem Cell Transplantation in Acute Leukemias

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Additional information is available at the end of the chapter

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Abstract

The chapter considers specific treatment options, including allogeneic hematopoietic stem cell transplantation (allo-HSCT) in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), in patients with some prognostically proven cytogenetic variants as monosomal ones, complex and hyperdiploid karyotypes, like chromosomal translocations t(v;11)(v;q23), t(3;3)/inv(3); t(8;21), t(9;22), etc. Important prognostic role of additional chromosome abnormalities was shown for the patients with t(8;21) and t(9;22). Hence, it is evident that allo-HSCT in patients with poor risk cytogenetic variant must be performed as early as possible, i.e., during first complete remission.

Keywords: leukemia, cytogenetic abnormalities, prognosis, allo-HSCT

1. Introduction

Acute leukemias represent a mixed group of malignant diseases with heterogeneous morphology, cytogenetics, and prognosis. From a genetic point of view, acute myeloid leukemias (AML) and acute lymphoblastic leukemias (ALL) consist of patients with favorable-, intermediate-, and poor-risk cytogenetic variants. A group of AML patients with favorable cytogenetics traits include those with translocations t(15;17), inv(16)/t(16;16), and t(8;21), whereas t(12;21) and high hyperdiploid karyotypes are associated with better prognosis in ALL patients. Currently, the group of AML patients with poor-risk cytogenetics includes cases with -7/7q-, -5/5q-, -17/17p-, t(3;3), t(6;9), t(v;11)(v;q23), monosomal, and complex karyotypes, whereas those with ALL exhibit mainly t(4;11) and t(9;22). Since a great part of AML and ALL patients are not cured by single chemotherapy, they need allogeneic hematopoietic stem cell

transplantation (allo-HSCT). So far, the results of allo-HSCT in patients with poor-risk and favorable-risk leukemias were analyzed in common cohorts [1, 2]. The aim of our work is to compare clinical outcomes of allo-HSCT for the patients with distinct cytogenetic variants.

2. Acute myeloid leukemia

2.1. AML with monosomal karyotype

One of the poor-risk chromosome abnormalities in AML patients is monosomal karyotype (MK), which is defined by the presence of one single autosomal monosomy in association with, at least, one additional autosomal monosomy or one structural chromosomal abnormality except for marker and ring chromosomes (**Figure 1**). MK is associated with a dismal prognosis and seems to be prognostically important even in complex karyotype AML. Breems et al. [3] were the first who have noted clinical significance of this finding. More recently, a strong association with *TP53* mutations was shown to be an important feature of this malignancy. Although *TP53* is only rarely affected in AML, it is the most frequently altered gene in complex and monosomal AML karyotypes. Hence, a conclusion was drawn that the loss-of-function of *TP53* might cause cytogenetic instability with subsequent development of complex karyotype alterations, but not *vice versa* [4]. Meanwhile, 5-year survival of the patients with this pathology did not exceed 5% [5], though 3-year survival in this group of AML patients may be increased from 5 to 19% following allo-HSCT [6]. A more favorable 4-year survival was achieved in a quarter of treated AML patients, if HSCT was performed at the first remission [7–9]. Additional analysis showed that the 5-year overall survival (OS) in transplanted patients was longer, as compared to those treated with single chemotherapy or by autologous transplantation (19% vs. 9%, respectively; $P = 0.02$). A similar trend seems to exist with respect

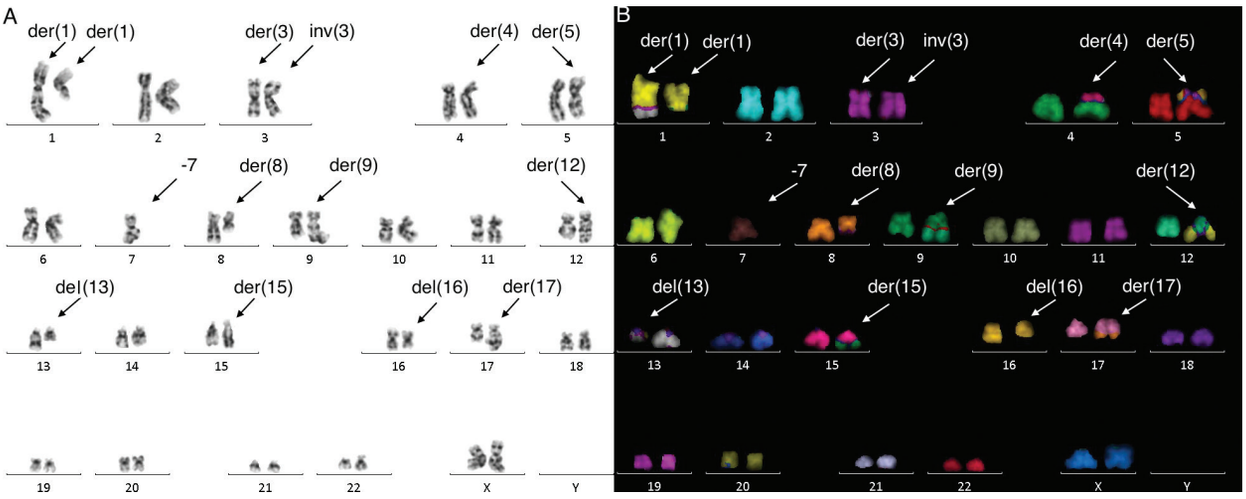

Figure 1. GTG-banded (A) and multicolor FISH (B) karyograms of bone marrow cells with complex and monosomal karyotype in acute myeloid leukemia patient. Karyotype: 45,XX,t(1;13)(q23;q14), der(1)t(1;9)(q21;?), der(3)t(3;5)(q?;?), inv(3)(q21q26),t(4;15)(p12;q22), der(5)t(5;16)(p?;q?)ins(5;3)(?;??),–7,t(8;17)(q22;q25), der(9)t(9;12)(q22;q13),der(12)t(1;12)(q21;q22) ins(12;9)(?;??),del(13)(q14),del(16)(q22).

to 5-year disease-free survival (DFS) or EFS (17% vs. 7%, $P = 0.003$). Multivariate analysis of these data revealed a strong correlation between lower relapse rates and prolonged EFS ($P < 0.001$). On the other hand, there was an only minimal difference in results of multivariate and intergroup analyses of posttransplant relapses and EFS between the groups with monosomal karyotypes and with other poor-risk cytogenetic aberrations. We have observed only eight patients with MK+, including 5q- and -7/7q-, in whom a 3-year disease-free survival was significantly lower than in MK− patients (13% vs. 27%, $P = 0.009$) [10]. Impact of MK upon the outcomes allo-HSCT performed at first remission was evaluated in 263 patients with AML [5]. First, there was a highly significant difference in 5-year OS ranging between 67%, for the most favorable, and 32%, for the poorest risk group ($P = 0.001$). Second, patients with non-MK abnormalities (MK−) and cytogenetically normal cases showed identical incidence of 5-year relapse (24%). Third, multivariate analysis revealed MK to be an independent prognostic factor, which was able to successfully predict OS (hazard ratios (HR) 3.74, $P = 0.01$) and relapse incidence (HR 3.74, $P = 0.005$), as compared to some other criteria, including those of SWOG/ECOG. Finally, subgroup analysis revealed prognostic ability of MK-based classification to be highly efficient in the patients treated with standard myeloablative conditioning prior to allo-HSCT ($P = 0.0011$ for OS, $P = 0.0007$ for relapse). However, the MK-based grouping failed to predict OS or incidence of relapse in HSCT patients treated with reduced intensity conditioning (RIC).

2.2. AML with complex karyotype

The interest to AML with CK as a distinct biological entity has appeared recently [7–11]. This anomaly is defined as three and more structural and numerical chromosome aberrations per metaphase (**Figure 1**), when excluding such recurring abnormalities, as t(8;21), inv(16)/t(16;16), t(15;17), or 11q23/MLL rearrangements [11–14]. Nowadays, it accounts for 10–20% of AML cases and increases sharply with age [15]. Despite intensive treatment, including allo-HSCT, median OS for these patients was <6 months and less than 10% patients achieved long-term survival [16]. It has been also established that incidence of CK+ cases in AML may increase after chemotherapy [17] and HSCT [18–20]. However, some recent data [21] suggested that a 90% CR rate was achieved for these poor-risk patients, if allo-HSCT was performed within 80–100 days after diagnosis even in active phase of the disease. A hypothetic explanation is that poor prognosis of AML patients with CK may be associated with a chromosomal instability which, in turn, is directly related to clonal evolution, selection, and adaptation of leukemic cells [3].

2.3. AML with hyperdiploid karyotype

Patients with hyperdiploid karyotypes (HDK) are not so rare in AML too, revealing many in common with aforementioned CK (**Figure 2**). For instance, in cases of sole chromosomes 8, 21, and 13 trisomies, these cases are classified as intermediate risk group. On the other hand, a new heterogeneous group with high hyperdiploidy and modal chromosome numbers from 49 to 65 has been recently described in about 2% of poor-risk AML patients [22], which was prognostically poor. Finally, cases with near triploid/tetraploid karyotype, especially associated

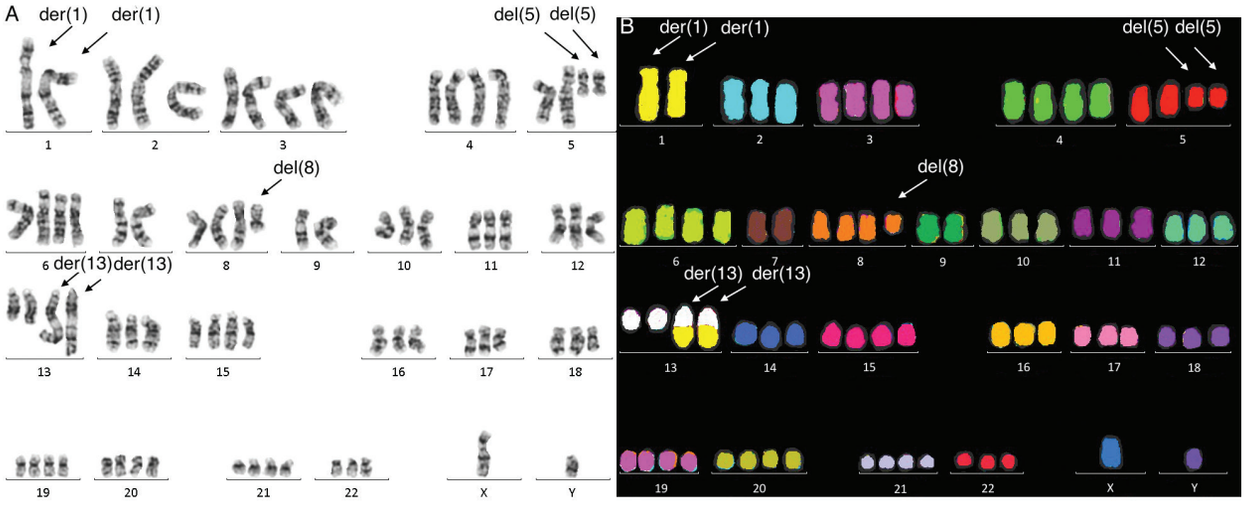

Figure 2. GTG-banded (A) and multicolor FISH (B) karyograms of bone marrow cells with hyperdiploid karyotype and adverse chromosome abnormality 5q– in acute myeloid leukemia patient relapsing after allo-HSCT. Karyotype: 75,<3n>,XY,–X,–1,der(1)del(1)(p32)ins(1;1)(q21;p32p36)x2,+3,+4,+5,del(5)(q13q33)x2,+6,–7,+8,del(8)(q11q23),–9,+13, der(13)t(1;13)(q21;q34)x2,+15,–17,+19,+20,+21,+22.

with structural chromosome anomalies are encountered not so often [23, 24]. Since there are no available publications concerning of allo-HSCT results in AML patients with HDK, we presented here our data on the topic in details [25]. Study group enrolled 47 AML patients (21 females, 26 males, aged 1–58 years; median age 23.9 years), in whom allo-HSCT was performed at our university during 2008–2015 years. Cytogenetic evaluation included standard GTG differential staining of chromosomes as well as Multicolor FISH (M-FISH), which were carried out according to standard manufacturer recommendations. Criteria for defining aberrations and nomenclature for description of the cytogenetic findings were in accordance to the international system for human cytogenetic nomenclature (ISCN) [26]. Allo-HSCT was performed in 13/47 (28%) patients in the first complete remission (CR), in 7/47 (15%) patients in the second CR, whereas 27/47 (57%) patients were transplanted in active disease. Sources of stem cells for the patients were as follows: bone marrow (n = 23; 49%) or peripheral blood stem cells ($n = 21$; 45%), while both were used in three (6%) patients. Reduced-intensity conditioning (RIC) regimen, including fludarabine, busulfan, and/or cyclophosphamide, as well as myeloablative regimen was used in 31 (66%) and 16 (34%) patients, respectively. HLA-related and nonrelated donors were used for nine (19%) and 32 (68%) patients, respectively. At the same time, related haploidentical allo-HSCT was performed for six (13%) patients. Thirty-one of 47 (66%) patients with HDK contained karyotypes with modal chromosome numbers of 47–48. A phenomenon of hyperdiploidy (49–65 chromosomes per metaphase) was revealed in 13/47 (28%) patients. At the same time in 3/47 (6%) patients, the modal numbers were near triploid and near tetraploid. Structural chromosome aberrations were revealed in 23/47 (49%) patients. Complex karyotypes with three or more chromosome anomalies were found in 19/47 (40%) patients, whereas the adverse chromosome abnormalities were registered in nine cases (19%). Numerical chromosomal anomalies were nonrandom. Trisomy 8 was the most common, being revealed in 22 patients (50%) patients excluding those with triploid and tetraploid karyotypes. It was as a single finding in seven (32%) patients while being combined with

other structural and numerical chromosome anomalies in 15 (68%) patients. In some patients, trisomy 8 was associated with t(6;9), monosomy 7, and abn(3q26), thus allowing to include them into the poor-risk cytogenetic group. The second position in the rate of trisomy incidence takes chromosome 21, which was revealed in 14 (32%) patients. It was observed as a single abnormality in seven (50%) patients, whereas in seven other cases (50%), the combination with additional chromosome abnormalities was noted. Of note, one patient exhibited a tetraploid set of chromosome 21. This is followed by chromosome 13 and 22 trisomies, which were revealed in seven patients each (16%). Trisomy 22 was found as single finding in two (29%) patients, in combination with the other chromosome abnormalities in five (71%) patients. Moreover, combination of trisomy 21 and del(11p) was noticed in one patient. Trisomy 13 was not presented alone, having been combined with other chromosome aberrations, with trisomy 19 and additional X chromosome in six (14%) and five (11%) patients, respectively. Numerical aberrations of chromosome 4 were less common, being revealed in four patients (9%), with a tetrasomic set in one case. Moreover, trisomy 7 and trisomy 6 were revealed in three (7%) and two (5%) patients, respectively. Finally, single findings of trisomy 3, 5, 9, 11, 12, 15, and 18 chromosomes as well as double Y were also documented. Chromosomal monosomy in AML patients with HDK was rare. Meanwhile, monosomy 18 was revealed in three (7%) patients from this subgroup. Three other patients had monosomies 2, 7, and 21. According to common classification the karyotypes of 19/47 (40%) may be designated as CK. They exhibited three or more chromosomal abnormalities coupled with, at least, one structural aberration. Poor-risk cytogenetic aberrations, e.g., -7/7q-, 5q-, anomalies 3q26, and 17p were revealed in 9/47 (19%) patients. This may be exemplified by a patient with tetraploid chromosome set associated with structural rearrangements including 5q- and other anomalies. Univariate analysis showed that OS and DFS after allo-HSCT significantly depend on clinical status of the patients' status at allo-HSCT ($P = 0.003$ and $P = 0.002$, respectively) as well as on the presence of adverse chromosome aberrations ($P = 0.002$ and $P = 0.01$, respectively). A significant difference in OS and DFS were revealed also in patients who were transplanted in the first or second remissions ($P = 0.04$ and $P = 0.04$, respectively). At the same time, the results of allo-HSCT did not depend on AML variant, patients' gender, donor's type, conditioning regime, source of HSC, as well as on modal number of chromosomes and presence or absence of structural rearrangements and complex aberrations in HDK. Using multivariate analysis, we have shown independent predictors for improved OS and DFS in AML patients with HDK, as following: (a) remission at allo-HSCT ($P = 0.003$ and $P = 0.021$, respectively); and (b) the absence of adverse chromosome aberrations ($P = 0.002$ and $P = 0.005$, respectively).

2.4. AML with *KMT2A (MLL)* rearrangement

AML with 11q23/*KMT2A* rearrangement is rare, and about 85 genes may be involved as partners for fusion with *KTM2A*. Most of these cytogenetic subtypes, except translocation of t(9;11)(p22;q23) [27], are classified into poor-risk cytogenetic group [28]. Predictive ability of this marker in HSCT setting was recently discussed [29, 30]. One of such recent studies [28] enrolled 138 patients with 11q23/*KMT2A*-rearranged AML, who were allografted in first or second CR. The cohort consisted of patients with t(9;11), t(11;19), t(6;9), and t(10;11) translocations. Two-year OS, leukemia-free survival, relapse incidence, and nonrelapse

mortality were 56 ± 4%, 51 ± 4%, 31 ± 3%, and 17 ± 4%, respectively. The 11q23.3 rearrangements causing *KMT2A (MLL)* exchanges of gene are revealed in about 3–7% of adult AML patients. Higher efficiency of allo-HSCT over chemotherapy alone in the treatment of AML patients with *KMT2A (MLL)* rearrangements seems to be evident [31].

2.5. AML with t(3;3)(q21;q26.2)/inv(3)(q21q26.2)

AML with inv(3)(q21q26.2)/t(3;3)(q21;q26.2) is a distinct subtype of AML with recurrent genetic abnormalities. It is commonly refractory to conventional chemotherapy due to *EVI1* gene overexpression, thus being associated with poor prognosis [32–36]. Isolated inv(3)/t(3;3) were revealed in 43.7% of such patients [33]. The most frequently observed additional cytogenetic abnormalities were: −7/del(7q) (37.3%), complex chromosome abnormality, and sometimes Ph+ chromosome [33]. Monosomy 7 is reported in approximately 40–60% of inv(3)/t(3;3) AML patients and associated with dismal prognosis [33–35]. Of interest is that AML and MDS patients with inv(3)/t(3;3) regardless of blast number have both similar clinical and pathological characteristics and short OS. Complex and monosomal karyotypes were also considered independent negative prognostic factors in AML patients with inv(3)/t(3;3) [36]. Due to low incidence of this poor-risk AML subtype, efficacy of HSCT is still subject to small clinical studies [34–36], mainly, with poor results. As an example of treatment failure in such cases, we presented a clinical case of a young female with inv(3)(q21q26.2), −7. The patient underwent a quantitative monitoring with serial expressions of *WT1* and *EVI* gene levels, as reported earlier [35]. The last large investigation in the field has been published recently [36]. It enrolled 32 transplanted patients in the first remission with overexpression of *EVI1* gene, induced by aberrations of 3q26 and 11q23 loci, and 119 control patients with low *EVI1* expression. The study showed much higher *EVI1*+ frequency in adverse-risk group, as compared with intermediate-risk group (53% vs. 19%, $P = 0.005$). The results of DFS and OS in 24 months of the *EVI1*+ cohort were shorter (52.6% vs. 71.0%, $P = 0.02$ and 52.8% vs. 72.4%, $P = 0.01$, respectively), whereas cumulative incidence of relapse was higher (39.5% vs. 22.5%, $P = 0.01$). Multivariate analysis revealed that low *EVI1* expression as an independent prognostic factor favoring DFS (HR = 0.47, 95% CI 0.26–0.86, $P = 0.01$) but not OS. These results indicated that high *EVI1* expression might predict high risk of relapse in AML patients undergoing myeloablative allo-HSCT in CR1.

2.6. AML with t(8;21)(q22;q22) *RUNX1/RUNX1T1*, inv(16)(p13q22)/t(16;16) *CBFβ/MYH11*

In view of the data concerning poor-risk AML groups, it would be interesting to discuss clinical outcomes after allo-HSCT in cohorts with favorable-risk cytogenetics. Several such studies should be mentioned [37–39]. The data revealed by Yoon et al. [40] consist of 264 adult patients with CBF-positive AML, where 206 of whom were in CR. Allo-HSCT was performed in 115 patients, whereas other patients were treated either by auto-HSCT ($n = 72$) or chemotherapy alone ($n = 19$). There was no difference in OS in groups of patients with *CBFβ/MYH11* ($n = 62$) and *RUNX1/RUNX1T1* ($n = 144$). Meanwhile, it was noted that OS was better in the patients treated by auto-HSCT, compared to those treated by either allo-HSCT or chemotherapy alone ($P = 0.001$). According to cytogenetic data, OS seems to be longer in patients with inv(16), which is not accompanied by trisomy. On the other hand, OS terms were shorter in patients with t(8;21) accompanied by additional chromosome aberrations.

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It should be mentioned that these findings were not supported by multivariate analysis. Molecular monitoring showed that OS was lower but incidence of posttransplant relapses proved to be higher in those patients with detectable minimal residual disease (MRD). Some other groups have recently reported on high number of additional chromosome and genetic abnormalities in patients with t(8;21), thus suggesting an impact on clinical outcome [41, 42]. We have recently yielded similar results in allo-HSCT patients with t(8;21) [43]. The study enrolled 25 *RUNX1-RUNX1T1*-positive AML patients (10 females and 15 males, age 2–58 years, a median of 20.2 years). The additional cytogenetic abnormalities were detected in 13 (52%) patients before the transplantation (**Figure 3**). CK with three or more chromosomal abnormalities were noticed in nine (69%) patients. The median follow-up was 566 (8–2127) days. Overall survival (OS) was 33% (95% CI 14–53) and relapse-free survival (RFS) was 26%

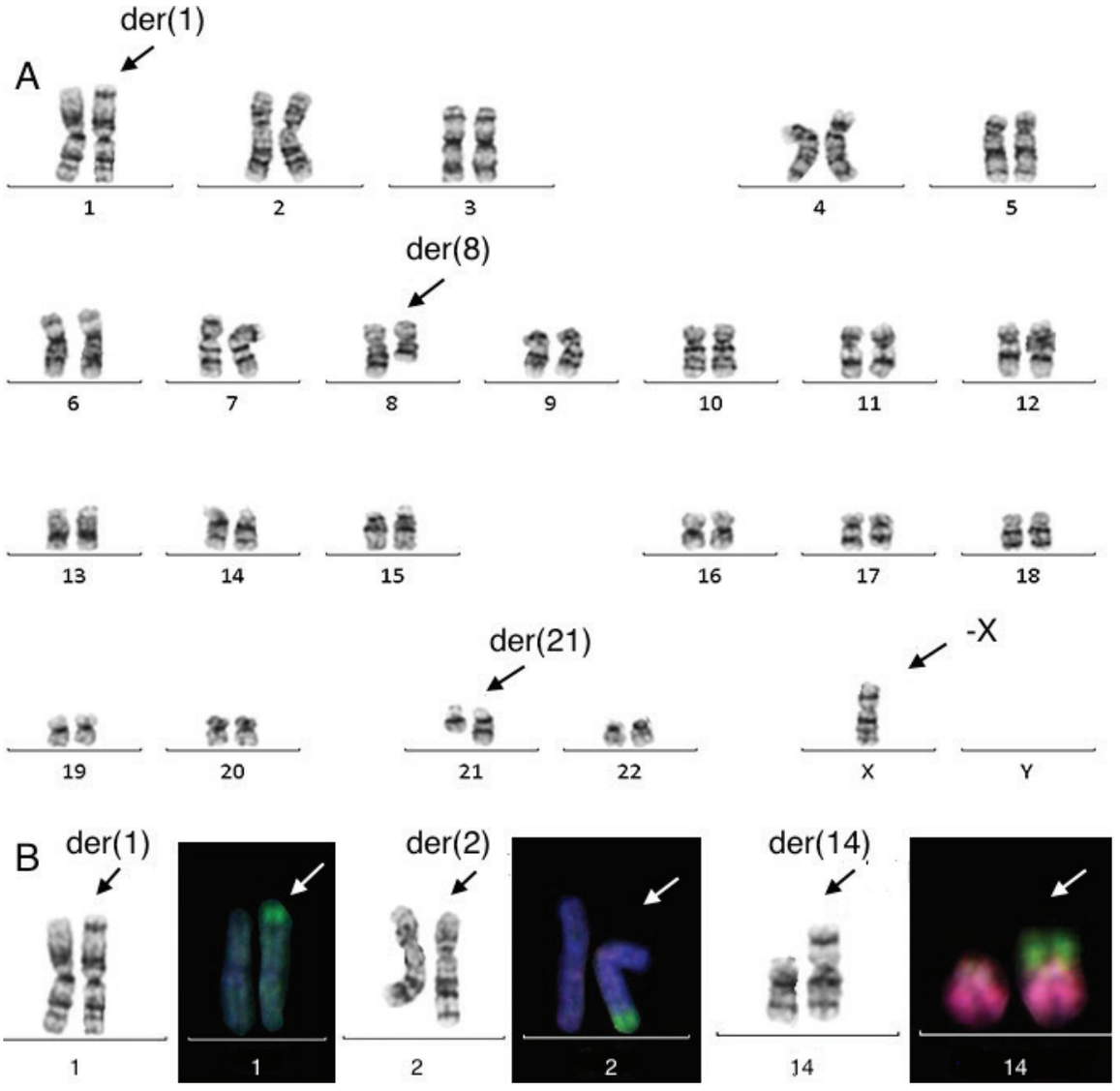

Figure 3. GTG-banded (A) and partial multicolor FISH (B) karyograms of bone marrow cells from AML patient demonstrate reciprocal translocation t(8;21)(q22;q22) and additional chromosome abnormalities, including "jumping" translocation 17q21-17qter followed by the production of derivative chromosomes #1, #2, #14. Karyotype: 45,X,-X,der(2)t(2;17)(q37;q21),t(8;21)(q22;q22)/45,X,-X, t(8;21),der(14)t(14;17)(p13;q21)/45,X,-X,der(1)t(1;17)(p36;q21),t(8;21).

(95% CI 9–45) at 4 years estimated with Kaplan-Meier method. The following factors predictive in univariate analysis for increased OS and RFS were: patients' age (>18 vs. <18 years; $P = 0.03$ and $P = 0.0006$, respectively), donor type (matched related/matched unrelated vs. haploidentical; $P = 0.0003$, $P = 0.02$, respectively), the disease status at transplant (complete remission vs. active disease; $P = 0.0002$ and $P = 0.005$, respectively), time interval from diagnosis to transplant (<360 vs. >360 days; $P = 0.008$, only for OS), ACA (ACA− vs. ACA+; $P = 0.02$ and $P = 0.009$, respectively), complex karyotype (CK− vs. CK+ ; $P = 0.004$ and $P = 0.0003$, respectively). In multivariate analysis, the ACA (HR 13.5; $P = 0.04$), the donor type (HR 6.86; $P = 0.01$), and time interval from diagnosis to HSCT (HR 6.80; $P = 0.02$) remained statistically significant for OS. Moreover, age (HR 0.11; $P = 0.004$) and the donor type (HR 4.16; $P = 0.04$) were independent predictors for RFS. On the basis of these findings, a conclusion may be drawn that AML with t(8;21)(q22;q22)/*RUNX1*/*RUNX1T1* translocation is a heterogeneous disease. The prognosis in patients with the additional cytogenetic abnormalities, especially in those with the CK, is worse both after the standard chemotherapy (i.e., before allo-HSCT) and after allo-HSCT as well.

3. Acute lymphoblastic leukemia

3.1. ALL with translocation t(9;22)(q34;q11.2) *BCR*/*ABL1*

Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) has been regarded for decades as the ALL subgroup with inferior outcome. However, introduction of tyrosine kinase inhibitors (TKI) in the induction treatment provided complete hematologic remissions (CHRs) in nearly all patients [44–51], thus allowing to recommend them as gold for Ph+ ALL patient's treatment. Together, these findings show that complete response to the therapy, including molecular remission, were achieved earlier in TKI-treated cohorts of ALL patients, whereas OS and DFS in these patients lasted longer than in a cohort that avoided TKI, regardless of their combinations with auto- or allo-HSCT. It has been also noticed that additional chromosome aberrations may be a poor predictor for the treatment results [51]**.** Three-year leukemia-free survival (79.8% vs. 39.5%, $P = 0.01$) and 3-year OS (83% vs. 45.6%, $P = 0.02$) were superior in the Ph+ only cohort compared with the ACA cohort ($n = 12$). Our recent data are in a good accordance with the above results, and supported the aforementioned opinion. The study was performed in 65 patients with Ph-positive ALL (26 female and 39 males aged 5–48 years, a mean of 26.2 years). Thirty-one (48%) and 20 (31%) patients were transplanted in the first or the second remissions, respectively, whereas 14 (21%) patients received transplant in active disease. The stem cell sources were bone marrow ($n = 31$; 49%) and peripheral blood cells ($n = 32$; 49%) or both ($n = 2$; 3%). Reduced-intensity conditioning regimen (RIC) was used in 36 (55%) patients, whereas myeloablative conditioning was applied in 29 (45%) patients. Cytogenetic evaluation at diagnosis was carried out in 53 (80%) patients. Ph-chromosome as a sole karyotype anomaly was detected in 33 (62%) patients. Due to high number of additional chromosomal changes (≥3) in a quarter of this group, they are described as "complex karyotypes" (**Figure 4**). HLA-related siblings were donors for 18 recipients (38%), whereas stem cells

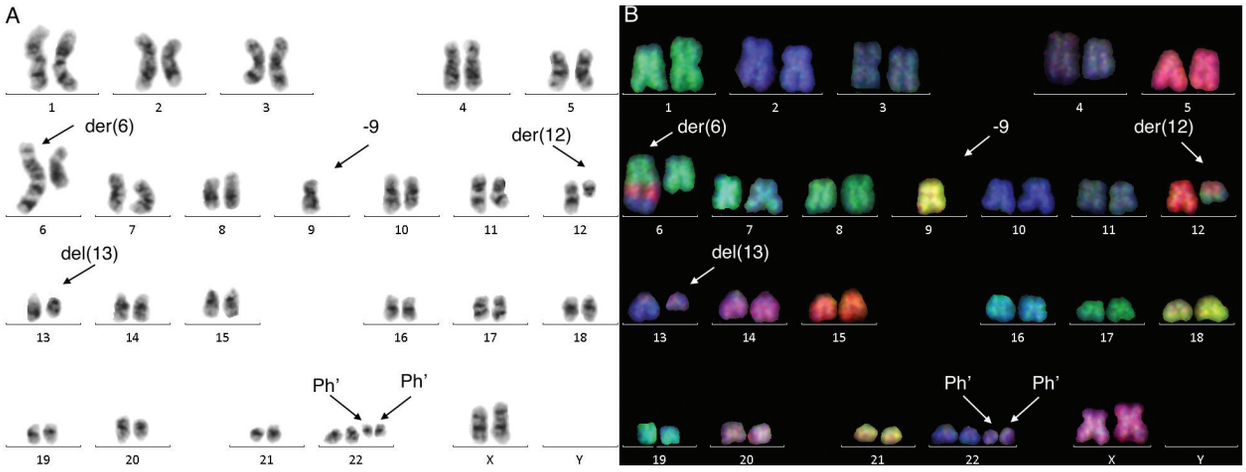

Figure 4. GTG-banded (A) and multicolor FISH (B) karyograms of bone marrow cells with translocation t(9;22)(q34;q11) and additional cytogenetic abnormalities in acute lymphoblastic leukemia patient relapsing after autological HSCT. Karyotype: 47,XX,der(6)t(6;13)(q23;q1?)ins(6;12)(q23;q13q24),-9,der(12) t(6;12)(q23;q13), del(13)(q1?),+22,+der(22)t(9;22)(q34;q11).

from HLA-matched nonrelated donors were used in 42 patients (65%). Moreover, five patients (7%) were transplanted with CD34+ cells from haploidentical family members. The number of CD34+ transfused cells ranged from 1.3 to 12.2 (mean 5.03) per kg of weight body. The study showed that additional chromosomal changes in Ph+ ALL were represented by numeric and/or structural abnormalities. Numeric changes were observed in 12 (60%) patients, affecting chromosomes 1, 2, 7, 8, 9, 10, 17, 19, and 22. Trisomy 1, 10, 22, and monosomy 7 were revealed in two patients each, whereas trisomy 2, 17, and 19 were revealed in single cases. The patterns and incidence of structural chromosome changes were as follows: deletions and translocations, involving 9p (n = 4; 20%); reciprocal translocations of 7p (n = 3; 15%), interstitial deletions/translocations of 5q (n = 4; 20%), deletions and translocations of chromosome 1 (n = 3; 15%) and 2 (n = 4; 20%), and structural aberrations of chromosome 17 (n = 2), including i(17q). Moreover, a double derivative of chromosome 22 was an additional chromosome abnormality in two patients. Univariate analysis revealed that 5-year OS was longer, when allo-HSCT was performed from HLA-matched related and unrelated donors (P = 0.02), when the patients had neither additional chromosome abnormalities in karyotypes (P = 0.04) nor primarily "complex" karyotypes (P = 0.01). On the other hand, DFS was longer in patients transplanted in the first remission (P = 0.01) with CD34-positive cells from completely matched donors (P = 0.02).

3.2. ALL patients with *KMT2A (MLL)* gene rearrangements

Structural rearrangements of 11q23.3 caused by inducing exchanges of *KMT2A (MLL)* gene are revealed in about 3–7% ALL patients, with up to 70–80% in newborn patients [28]. The main of these translocations—t(4;11)(q21;q23) *KMT2A/AFF1* [52]—occurs in 8–10% of ALL cases with a peak of incidence in infants. Despite generally poor prognosis for ALL with t(4;11) in all pediatric patients, it is the worst for infants [53–55]. Because of absent for this category of patient a targeted drug, allo-HSCT remains a single curative treatment [53]. According to recent findings, 5-year OS

reached 67.4% in newborns with *KMT2A*+ ALL, subjected to earlier performed allo-HSCT in first remission [56–58]. Such curative effect did not depend on patient's age, initial leukocytosis, cytogenetic findings, donor type, and options of conditioning regimen, although myeloablative conditioning with Busulfan seems to be preferable in these cases. Multivariate analysis showed the number of transfused mononuclear donor cells to be a basic predictor for longer OS ($P = 0.04$). To our knowledge, only one survey concerned results of allo-HSCT in adult patients with t(4;11) [31]. In general, allo-HSCT was performed in 56 patients, including 46 patients over 15 years old, and 10 children. Twenty-nine patients (7–64 years old) were enrolled for autologous HSCT or chemotherapy alone, as a comparison group. Despite it, all tested patients showed myeloid engraftment. Overall, posttransplant relapses were diagnosed in 12 transplanted patients after a median of 208 days, reaching a cumulative incidence of hematological relapse of 25.3% at 3 years. Additional analysis showed that 6/41 (14.6%) transplanted in CR1 and 6/15 (40%) patients with non-CR1 status at transplantation relapsed after HSCT ($P = 0.04$). Univariate analysis showed that the 3-year CIR was 48.1 and 17.9% for the patients transplanted in CR1 and non-CR1 status, respectively ($P = 0.03$). In multivariate analysis, CR1 status at transplantation proved to be the only predictor of lower relapse rate ($P = 0.018$). Noteworthy, 37 patients were alive at the last follow-up, with a median survival time of 742 (range 172–1866) days after HSCT without recurrence of the disease. The probabilities for OS and DFS were 61.8 and 56.3% at 3 years, respectively, after HSCT. Adults and children had comparable OS and DFS rates. The patients who received nucleated cells above the median level had higher OS than the recipients transplanted at smaller cell doses (72.2% vs. 39.2%, $P = 0.02$). The predictive value of MNC numbers was mainly attributed to peripheral blood graft. Specifically, since patients receiving more nucleated cells in peripheral blood graft had higher OS than the patients, who received lower MNC quantities (65.8% vs. 42.9%, $P = 0.03$). In multivariate analysis higher MNC doses were found to be the only predictor for higher OS with hazard ratio (HR) of 0.34 (95% CI, 0.12–0.98, $P = 0.04$). In our recent study, HSCT was performed at the first or the second remissions in 11 (44%) and three (12%) patients, respectively, whereas 11 (44%) patients were transplanted in relapse state. This group included 21 patients with t(4;11)(q21;q23) *KMT2A*/*AFF1* and four recipients with variant translocations at 11q23 locus. Translocation t(4;11)(q21;q23) was the "sole" finding only in 10 (48%) patients. In 11 patients (52%), it was associated with other structural changes, i.e., del(1), del(3p), i(7q), i(17q), and der(19p). It should be also mentioned that seven patients had each ≥3 chromosome aberrations, thus allowing to place them to the group with "complex" karyotype. Rearrangements of chromosomes 1, 7, and 3 should be mentioned as additional chromosomal aberrations (in 5, 4, and 3 patients, respectively). Stem cells sources were bone marrow (n = 7), peripheral blood (n = 17), or both ($n = 1$). Reduced-intensity ($n = 13$; 52%) or myeloablative ($n = 12$; 48%) conditioning regimens were used for HSCTs. Donors were HLA-matched related or matched unrelated (6 and 11 patients, respectively). On the other hand, in eight (32%) patients haploidentical transplantation was performed. Univariate analysis confirmed the existing view that OS and DFS of patients with KMT2A involvement was significantly longer, when HSCT was performed in complete remission regardless of the first or the second remission ($P = 0.0001$), and if other sources than peripheral blood were used for HSCT ($P = 0.01$ and $P = 0.07$ for OS and DFS, respectively). Finally, DFS was shorter in patients with additional chromosome abnormalities in karyotypes ($P = 0.05$), especially with CK ($P = 0.01$). Data from multivariate analysis supported conclusions drawn by previous investigators demonstrating a favorable influence of CR status on HSCT outcomes only on outcome of HSCT in adult ALL patients with 11q23 abnormality.

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4. Conclusion

Analysis of the HSCT results in patients with prognostically different cytogenetic variants of acute leukemias showed that this approach may be efficient in all the tested patients and that it can be effective enough in all tested cohorts, including patients with the most poor-risk leukemias with monosomal and complex karyotypes, as well as those with translocations t(4;11)(q21;q23), t(9;22)(q34;q11.1), t(3;3)(q21;q26.2), etc. The situation can be dramatically changed with the introduction of highly effective targeted drugs, e.g., TKIs, into therapeutic protocols for Ph-positive leukemias.

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References

[1] Armand P, Kim HT, De Angelo DJ, et al. Impact of cytogenetics on outcome of de novo and therapy-related AML and MDS after allogeneic transplantation. Biol Blood Marrow Transplant. 2007:13:655-664. DOI: 10.1016/jbbmt.2007.01.079

[2] Nahi H, Remberger M, Machaczka M, et al. Different impact of intermediate and unfavorable cytogenetics at the time of diagnosis of de novo AML after allo-SCT: a long-term retrospective analysis from a single institution. Med Oncol. 2012;29:2348-2358. DOI: 10.1007/s12032-011-0155-y

[3] Breems DA, Van Putten WLL, De Greef GE, et al. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. J Clin Oncol. 2008;26:4791-4797. DOI: 10.1200/jco.2008.16.0259

[4] Bochtler T, Fröhling S, Krämer A, et al. Role of chromosomal aberrations in clonal diversity and progression of acute myeloid leukemia. Leukemia. 2015;29:1243-1252. DOI: 10.1038/leu.2015.32

[5] Hemmati PG, Schulze-Luchkov A, Terwey ThN, et al. Cytogenetic risk grouping by the monosomal karyotype classification is superior in predicting the outcome of acute myeloid leukemia undergoing allogeneic stem cell transplantation in complete remission. Eur J Haematol. 2013;92:102-110. DOI: 10.1111/ejh.12216

[6] Oran B, Dolan M, Cao Q, et al. Monosomal karyotype provides better prognostic prediction after allogeneic stem cell transplantation in patients with acute myelogenous leukemia. Biol Blood Marrow Transplant. 2011;17:356-364. DOI: 10.1016/j.bbmt.2010.05.012

[7] Fang M, Storer B, Estey E, et al. Outcome of patients with acute myeloid leukemia with monosomal karyotype who undergo hematopoietic stem cell transplantation. Blood 2011;118:1490-1494. DOI: 10.1182/blood-2011-02-339721

[8] Cornelissen JJ, Breems D, van Putten WL, et al. Comparative analysis of the value of allogeneic hematopoietic stem-cell transplantation in acute myeloid leukemia with monosomal karyotype versus other cytogenetic risk categories. J Clin Oncol. 2012;30:2140-2146. DOI: 10.1200/jco.2011.39.6499

[9] Pasquini M, Zhang M-J, Medeiros BC, et al. Hematopoietic cell transplantation outcomes in monosomal karyotype myeloid malignancies. Biol Blood Marrow Transplant. 2016;22:248-257. DOI: 10.1016/j.bbmt.2015.08.024

[10] Gindina TL, Mamaev NN, Bondarenko SN, et al. Allogeneic hematopoietic stem cell transplantation in acute myeloid leukemias: prognostic significance of complex karyotype including del(5q), -7, del(7q) abnormalities. Clin Oncohematol. 2016;9:271-278. DOI: 10.21320/2500-2139-2016-9-3-271-278 [In Russ].

[11] Schoch C, Kern W, Kohlmann A, et al. Acute myeloid leukemia with a complex aberrant karyotype is a distinct biological entity characterized by genomic imbalance and a special gene expression profile. Genes Chromosomes Cancer. 2005;43:227-238. DOI: 10.1002/gcc.20193

[12] Mrozek K. Cytogenetic, molecular genetics, and clinical characteristics of acute myeloid leukemia with a complex karyotype. Semin Oncol. 2008;358:365-377. DOI: 10.1053/j.seminoncol.2008.04.007

[13] Dobbelstein C, Dammann E, Weissinger E, et al. Prognostic impact a newly defined structurally complex karyotype in patients with AML and MDS after allogeneic stem cell transplantation [abstract]. Blood. (Ash Ann. Meet. Abstr.) 2013;122:3362-3363.

[14] Gindina TL, Mamaev NN, Bondarenko SN, et al. Complex chromosomal aberrations in patients with post-transplantation relapses of acute leukemias: clinical and theoretical aspects. Clin Oncohematol. 2015;5:69-77 [In Russ].

[15] Fleischman EW, Sokova OI, Popa AV, et al. Complex karyotype in paediatric acute myeloid leukemia. Clin Oncohematol. 2015;8:151-160 [In Russ].

[16] Zaccaria A, Rosti G, Testoni N, et al. Chromosome studies in patients with nonlymphocytic or acute lymphocytic leukemia submitted to bone marrow transplantation – results of European cooperative study. Cancer Genet Cytogenet. 1987;26:51-58. DOI: 10.1016/0165-4608(87)90132-4

[17] Schmidt-Hieber M, Blau IW, Richter G, et al. Cytogenetic studies in acute leukemia patients relapsing after allogeneic stem cell transplantation. Cancer Genet Cytogenet. 2010;198:135-143. DOI: 10.1016/j.cancergencyto. 2010.01.005

[18] Gindina TL, Mamaev NN, Barkhatov IM, et al. Complex chromosome damages in patients with recurrent acute leukemias after allogeneic hematopoietic stem cell transplantation. Ther Arkhiv. 2012;8:61-66 [In Russ].

[19] Chi H.S, Cho YU, Park SH, et al. Comparative analysis of cytogenetic evolution patterns during relapse in the hematopoietic stem cell transplantation and chemotherapy settings of patients with acute leukemia [abstract]. Blood. (Ash Ann. Meet. Abstr.) 2013;122:1320-1320.

[20] Yuasa M, Uchida M, Kaji D, et al. Prognostic significance of the cytogenetic evolution after the hematopoietic stem cell transplantation in adult acute myeloid leukemia [abstract]. Blood. (Ash Ann. Meet. Abstr.) 2013;122:1391-1391.

[21] Schmid C, Schleuning M, Tischer J, et al. Early allo-SCT for AML with a complex aberrant karyotype – results from a prospective pilot study. Bone Marrow Transplant. 2012;47:46-53. DOI: 10.1038/bmt.2011.15

[22] Chilton L, Hills RK, Harrison CJ, et al. Hyperdiploidy with 49-65 chromosomes represents a heterogeneous cytogenetic subgroup of acute myeloid leukemia with differential outcome. Leukemia. 2013;28:321-328. DOI: 10.1038/leu.2013.198

[23] Lazarus HM, Litzow MR. AML cytogenetics: the complex just got simpler. Blood. 2012;120:2357-2358. DOI: 10.1182/blood-2012-08-448555

[24] Pang CS, Pettenati MJ, Pardee TS, et al. Clinicopathological analysis of near-tetraploidy/tetraploidy acute myeloid leukemia. J Clin Pathol. 2015;68:236-240. DOI: 10.1136/clinpathol-2014-202697

[25] Gindina TL, Mamaev NN, Nikolaeva ES, et al. Outcome of allogeneic hematopoietic stem cell transplantation in acute myeloid leukemias with hyperdiploid karyotype. Clin Oncohematol. 2016;9:383-390. DOI: 10.21320/2500-2139-2016-9-4-383-390 [In Russ].

[26] Schaffer LG, McGovan-Jordan J, Schmid M. ISCN. An International System for Human Cytogenetic Nomenclature. Basel: Karger, 2013: 140 p.

[27] Mrozek K, Heinonen K, Lawrence D, et al. Adult patients with de novo acute myeloid leukemia and t(9;11)(p22q23) have a superior outcome to patients with other translocations involving band 11q23: a cancer and a leukemia group B study. Blood. 1997;90: 4532-4538.

[28] Wang Y, Liu QF, Qin YZ, et al. Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of patients with mixed-lineage-leukemia-rearranged acute leukemia: results from a prospective, multicenter study. Am J Hematol. 2014;89:130-136. DOI: 10.1002/ajh.23593

[29] Chen Y, Kantarjian H, Pierce S, et al. Prognostic significance of 11q23 aberrations in adult acute myeloid leukemia and the role of allogeneic stem cell transplantation. Leukemia. 2013;27:836-842. DOI: 10.1038/leu.2012.319

[30] Pigneux A, Labopin M, Maertens J, et al. Outcome of allogeneic hematopoietic stem-cell transplantation in adult patients with AML and 11q23/MLL rearrangement (MLL-r-AML). Leukemia. 2015;29:2375-2381. DOI: 10.1038/leu.2015.143

[31] Yang H, Huang S, Zhu C-Y, et al. The superiority of allogeneic hematopoietic stem cell transplantation over chemotherapy alone in the treatment of acute myeloid leukemia patients with mixed lineage leukemia (MLL) rearrangements. Med Sci Monit. 2016;22:2315-2323. DOI: 10.12659/MSM.899186

[32] Lugthart S, Groeschel S, Beverloo HB, et al. Clinical, molecular, and prognostic significance of WHO type inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and various other 3q abnormalities in acute myeloid leukemia. J Clin Oncol. 2010;28:3890-3898. DOI: 10.1200/JCO.2010.29.2771

[33] Rogers HJ, Vardiman JW, Anastasi J, et al. Complex or monosomal karyotype and not blast percentage is associated with poor survival in acute myeloid leukemia and myelodysplastic syndrome patients with inv(3)(q21q26.2)/t(3;3)(q21;q26.2): a Bone Marrow Pathology Group study. Haematologica. 2014;99:821-829. DOI: 10.3324/Haematol.2013.096420

[34] Mamaev NN, Gorbunova AV, Gindina TL, et al. Leukemias and myelodysplastic syndromes with high *EVI1* gene expression: theoretical and clinical aspects. Clin Oncohematol. 2012;5:361-364 [In Russ].

[35] Mamaev NN, Gorbunova AV, Gindina TL, et al. Stable donor hematopoiesis reconstitution after post-transplanation relapse of acute myeloid leukemia in patient with inv(3)(q21q26),–7 and EVI1 overexpression treated by donor lymphocyte infusions and hypomethylating agents. Clin Oncohematol. 2014;7:71-76 [In Russ].

[36] He X, Wang Q, Cen J, et al. Predictive value of high *EVI1* expression in AML patients undergoing myeloablative allogeneic hematopoietic stem cell transplantation in first CR. Bone Marrow Transplant. 2016;51;921-927. DOI: 10.1038/bmt.2016.71

[37] Schlenk RF, Pasquini MC, Perez WS, et al. HLA-identical sibling allogeneic transplant versus chemotherapy in acute myelogenous leukemia with t(8;21) in first complete remission : collaborative study between the German AML intergroup and CIBMTR. Biol Blood Marrow Transplant. 2008;14:187-196. DOI: 10.1016/j.bbmt.2007.10.006

[38] Kuwatsuka Y, Miyamura K, Suzuki R, et al. Hematopoietic cell transplantation for core binding factor acute myeloid leukemia; t(8;21) and inv(16) represent different clinical outcomes. Blood. 2009;113:2096-2103. DOI: 10.1182/blood-2008-03-145862

[39] Numata A, Fujimaki K, Aoshima T, et al. Retrospective analysis of treatment outcomes in 70 patients with t(8;21) acute myeloid leukemia. Rinsho Ketsueki. 2012;53:698-704.

[40] Yoon JH, Kim HJ, Kim JW, et al. Identification and cytogenetic risk factors for unfavorable core-binding factor–positive adult AML with post-remission treatment outcome analysis including transplantation. Bone Marrow Transplant. 2014;49:1466-1474. DOI: 10.1038/bmt.2014.180

[41] Krauth MT, Eder C, Alpermann T, et al. High number of additional genetic lesions in acute myeloid leukemia with t(8;21)/RUNX1-RUNX1T1: frequency and impact on clinical outcome. Leukemia. 2014;28:1449-1458. DOI: 10.1038/leu.2014.4

[42] Klein K, Kaspers G, Harrison CJ, et al. Clinical impact of additional cytogenetic aberrations, cKIT and RAS mutations and treatment elements in paediatric t(8;21)-AML: results from an international retrospective study by the international Berlin-Frankfurt-Munster study group. J Clin Oncol. 2015;33:4247-4258. DOI: 10.1200/jco.2015.61.1947

[43] Gindina TL, Mamaev NN, Bondarenko SN, et al. Results of allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia with t(8;21)(q22;q22)/*RUNX-RUNX1t1* and additional cytogenetic abnormalities. Clin Oncohematol. 2016;9:148-154. DOI: 10.21320/2500-2139-9-2-148-154 [In Russ].

[44] Parma M, Vigano C, Fumagalli M, et al. Good outcome for very risk adult B-cell acute lymphoblastic leukemia carrying genetic abnormalities t(4;11)(q21;q23) or t(9;22)(q34;q11), if promptly submitted to allogeneic transplantation after obtaining a good molecular remission. Mediterr J Hematol Infect Dis. 2015;7:e2015041. DOI: 10.4084/MJHID.2015.041

[45] Ribera JM, Oriol A, Gonzalez M, et al. Concurrent intensive chemotherapy and imatinib before and after stem cell transplantation in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia: final results of the CSTIBES02 trial. Haematologica 2010;95:87-95. DOI: 10.3324/haematol.2009.011221

[46] Ribera JM, García O, Montesinos P, et al. Treatment of young patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia using increased dose of imatinib and deintensified chemotherapy before allogeneic stem cell transplantation. Br J Haematol. 2012;159:78-81. DOI: 10.1111/j.1365-2141.2012.09240.x

[47] Kebriaei P, Saliba R, Rondon G, et al. Long-term follow-up of allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome positive acute lymphoblastic leukemia: impact of tyrosine kinase inhibitors on treatment outcomes. Biol Blood Marrow Transplant. 2012;18:584-592. DOI: 10.1016/j.bbmt.2011.08.011

[48] Armand P, Kim HT, Zhang MJ, et al. Classifying cytogenetics in patients with acute myelogenous leukemia in complete remission undergoing allogeneic transplantation: a Center for International Blood and Marrow Transplant Research study. Biol Blood Marrow Transplant. 2012;18:280-288. DOI: 10.1016/j.bbmt.2011.07.024

[49] Fielding AK, Rowe JM, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood. 2014;123:843-850. DOI: 10.1182/blood-2013-09-529008

[50] Chiaretti S, Foa R. Management of adult Ph-positive acute lymphoblastic leukemia. Hematology. Am Soc Hematol Educ Prog. 2015;2015:406-415. DOI: 10.1182/asheducation-2015.1.406

[51] Aldoss I, Stiller T, Cao TM, et al. Impact of additional cytogenetic abnormalities in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia undergoing allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2015;21:1326-1329. DOI: 10.1016/j.bbmt.2015.03.021

[52] Sanjuan-Pla A, Bueno C, Prieto C, et al. Revisiting the biology of infant t(4;11)/MLL-AF41 B-cell acute lymphoblastic leukemia. Blood. 2015;126:2676-2685. DOI: 10.1182/blood-2015-09-967378

[53] Kosaka Y, Koh K, Kinukawa N, et al. Infant acute lymphoblastic leukemia with MLL gene arrangements: outcome following intensive chemotherapy and hematopoietic stem cell transplantation. Blood. 2004;104:3527-3534. DOI: 10.1182/blood-2004-04-1390

[54] Mann G, Attarbaschi A, Schrappe M, et al. Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study. Blood. 2010;116:2644-2650. DOI: 10.1182/blood-2010-03-0273532

[55] Dreyer ZE, Dinndorf PA, Camitta B, et al. Analysis of the role of hematopoietic stem-cell transplantation in infants with acute lymphoblastic leukemia in first remission and MLL gene rearrangements: a report from the Children's Oncology Group. J Clin Oncol. 2011;29:214-222. DOI: 10.1200/jco.2009.26.8938

[56] Tomizava D, Kato M, Takahashi H, et al. Favourable outcome in non-infant children with MLL-AF4-positive acute lymphoblastic leukemia: a report from the Tokyo Children's Cancer Study Group. Int J Hematol. 2015; 102:602-610. DOI: 10.1007/s12185-015-1869-y

[57] Kato M, Hasegawa D, Koh K, et al. Allogeneic haematopoietic stem cell transplantation for infant acute lymphoblastic leukemia with KMT2A (MLL) rearrangements: a retrospective study from the pediatric acute lymphoblastic leukemia working group of the Japan Society for Haematopoietic Cell Transplantation. Br J Haematol. 2014;4:564-570. DOI: 10.1111/bjh.13174

[58] Koh K, Tomozawa D, Saito AM, et al. Early use of allogeneic hematopoietic stem cell transplantation for infants with MLL gene rearrangement-positive acute lymphoblastic leukemia. Leukemia. 2015;29:290-296. DOI: 10.1038/leu.2014.172