Acute leukemia and myelodysplasia after adjuvant chemotherapy for breast cancer: durable remissions after hematopoietic stem cell transplantation

V. Pullarkat1*, M. L. Slovak2, A. Dagis3, V. Bedell2, G. Somlo1, R. Nakamura1, A. S. Stein1, M. R. O’Donnell1, A. Nademanee1, A. L. Teotico1, S. Bhatia4 & S. J. Forman1

1Division of Hematology and Hematopoietic Cell Transplantation; 2Department of Cytogenetics; 3Division of Biostatistics and 4Division of Population Sciences, City of Hope National Medical Center, Duarte, CA 91010, USA

Received 31 October 2008; revised 26 February 2009; accepted 17 March 2009

Background: Although secondary acute leukemias and myelodysplasia are the known complications of adjuvant chemotherapy for breast cancer, the treatment outcome of these secondary malignancies is presently unclear. We examined the clinical and pathological features as well as the treatment results of a series of patients with acute leukemia/myelodysplasia arising after adjuvant chemotherapy for breast cancer.

Patients and methods: Patients referred to our institution during a 5-year period for treatment of acute leukemia/myelodysplasia and who had received adjuvant chemotherapy for breast cancer are included. Leukemia-free survival for the whole group and for patients who underwent hematopoietic stem cell transplantation (HSCT) was estimated.

Results: Fifteen women (14 with acute leukemia and one with myelodysplasia) were identified. Seven of 15 patients had received an anthracycline, cyclophosphamide and a taxane. Ten patients developed acute leukemia/myelodysplasia with a latency period of 2 years or less from initiation of chemotherapy. Although mixed-lineage leukemia (MLL) rearrangement was the commonest chromosomal abnormality (8 of 15 patients), various other chromosomal abnormalities were also detected. Twelve of 15 patients underwent HSCT (11 allogeneic and one autologous). Eleven of these 12 patients who underwent HSCT were in remission at a median follow-up of 20.4 months (range 4.4–53.3 months).

Conclusion: Durable remissions can be achieved in patients who develop acute leukemia/myelodysplasia secondary to adjuvant chemotherapy for breast cancer and are able to undergo allogeneic HSCT. Our results indicate that HSCT should be an early consideration in the management of such patients who are suitable candidates for the procedure.

Key words: acute leukemia, adjuvant chemotherapy, breast cancer, myelodysplasia, therapy related

introduction

The outcome of early-stage breast cancer has been considerably improved in recent years with the development of effective adjuvant combination chemotherapy, which prolongs disease-free and overall survival [1]. The majority of patients with early-stage breast cancer whose tumors exceed 1 cm in size currently receive adjuvant chemotherapy that most often includes cyclophosphamide and an anthracycline with or without a taxane [2, 3]. Patients who chose to undergo lumpectomy will in addition receive radiation therapy for locoregional disease control.

Secondary leukemia and myelodysplasia result from chemotherapy or radiation therapy-induced hematopoietic stem cell damage and is arguably the most serious long-term consequence of chemotherapy and radiation therapy [4]. Translocations involving the mixed-lineage leukemia (MLL) gene on chromosome band 11q23 are a hallmark of therapy-related acute leukemia and myelodysplasia that results from treatment with topoisomerase II inhibitors, which includes the anthracyclines [4, 5]. These translocations of the MLL gene result in its fusion with a variety of partner genes resulting in aberrant gene expression in hematopoietic stem cells and development of leukemia [6]. Other abnormalities including MLL partial tandem duplication, MLL amplification, core-binding factor (CBF) and PML-RAR-α translocations have also been described in therapy-related leukemia [4, 7–11].

The incidence of secondary leukemias after nonanthracycline-based adjuvant chemotherapy regimens for breast cancer appears to be low [2, 4]. However, the precise incidence and treatment outcome of such hematologic malignancies occurring secondary to currently used
patients and methods

The study was approved by the Institutional Review Board of City of Hope Medical Center. Patients referred to City of Hope Medical Center during a 5-year period from 2001 to 2006 for the treatment of myelodysplasia or acute leukemia and who had received adjuvant chemotherapy for breast cancer are included in this report. Patients who had undergone high-dose chemotherapy followed by autologous stem cell transplantation as adjuvant therapy are excluded. Whenever possible, cytogenetic studies carried out at outside laboratories were confirmed at our institution by FISH analysis on fresh or archived specimens using standard methods. Survival curve for leukemia-free survival was drawn using the Kaplan–Meier estimator.

results

Fifteen women who met the above criteria were identified. Their clinical and pathological features are summarized in Table 1. Patients ranged in age from 32 to 66 years. Anthracycline (doxorubicin or epirubicin), cyclophosphamide and taxane (paclitaxel or docetaxel) were the commonest chemotherapy regimen used (seven patients) followed by cyclophosphamide, methotrexate and 5-fluorouracil in three patients, doxorubicin and cyclophosphamide in two patients and cyclophosphamide, doxorubicin and 5-fluorouracil in three patients.

Thirteen patients received radiation therapy. The latency period from the initiation of chemotherapy to the diagnosis of the secondary malignancy ranged from 9 months to >7 years. Ten patients had a latency period of 2 years or less from initiation of chemotherapy.

There were 13 patients with acute myeloid leukemia (AML), one patient with myelodysplastic syndrome and another with precursor B-cell acute lymphoblastic leukemia. MLL gene rearrangement was the commonest chromosomal abnormality and was detected in eight patients. One of the AML cases had acute promyelocytic leukemia (APL) with a cryptic MLL rearrangement, confirmed to be an insertion of the RAR-α gene into the derivative chromosome 15 by FISH analysis. One patient each had inv(16), trisomy 8, t(8;16) and t(9;22). In the patient with trisomy 8 (case 14), sufficient material was not available to exclude a variant (8;21). Two patients had AML with normal cytogenetics. One AML patient presented with myeloid sarcoma of the uterus without concurrent leukemia. MLL gene rearrangement was demonstrated in this patient by paraffin-embedded FISH analysis of tumor tissue. The details of this case have been published elsewhere [12].

The details of treatment for breast cancer and the secondary hematologic malignancy are summarized in Table 1. One patient died of sepsis after induction therapy and another two patients died of progressive disease before HSCT. Twelve of 15 patients underwent HSCT. Morphologic complete remission (CR) after induction chemotherapy was achieved in 9 of 11 patients with acute leukemia who underwent HSCT. Busulfan–cyclophosphamide and fludarabine–melphalan were the commonest conditioning regimens and were used in six and four patients, respectively. Five patients each received matched sibling donor and matched-unrelated donor HSCT while one patient each received autologous and double umbilical cord blood HSCT.

One patient died at 2.6 months after having relapsed at 2.4 months post-transplant. Another patient relapsed at 4.1 months after allogeneic HSCT, but was reinduced into CR with 5-azacytidine and remains in complete remission at 20 months of follow-up since HSCT. Median follow-up of the 11 transplanted patients currently alive is 20.4 months (range 4.4–53.3 months). Median follow-up of the 10 patients in continuous remission is 20.9 months (range 4.4–53.3 months). The leukemia-free survival of all patients as well as the 12 patients who underwent HSCT is shown in Figure 1.

discussion

The cases reported here illustrate the spectrum of chromosomal abnormalities that occurs in hematologic malignancies that occur after adjuvant chemotherapy for breast cancer. Although MLL gene rearrangements were by far the commonest, a variety of other chromosomal aberrations were present including CBF translocations, t(15;17) and trisomy 8. As would be expected for secondary leukemias related to topoisomerase II inhibitor therapy, our cases are notable for the short latency after chemotherapy in most patients, in some cases as early as within the first year after initiation of chemotherapy. Durable remissions were achieved in 11 of 12 patients who were able to undergo HSCT.

Secondary acute leukemia/myelodysplasia with an 11q23/MLL gene rearrangement is a well-described complication of anthracycline-based adjuvant chemotherapy for breast cancer. The median latency for development of these malignancies was 24 months in one study [13]. Translocations involving 11q23/MLL have generally been attributed to the topoisomerase II inhibitor activity of anthracyclines in the case of adjuvant breast cancer therapy. However, various factors appear to modulate the leukemogenicity of anthracyclines including addition of alkylating agents and/or radiation [13, 14]. Although MLL rearrangements typically manifest as AML or myelodysplasia, rarely manifestations such as acute lymphoblastic leukemia or isolated myeloid sarcoma may occur as illustrated by individual patients in this report.

Other leukemias that have been reported in the therapy-related setting are AML with CBF translocations namely t(8;21) and inv(16)/t(16;16), AML with RUNX1 (AML1) mutations and APL [8, 10, 15, 16]. A variety of point mutations have also been reported in therapy-related AML and myelodysplasia [17]. The role of topoisomerase II inhibitors in the pathogenesis of t(8;21) and t(15;17) AML has been shown in studies that demonstrate clustering of DNA breakpoints in these translocations with topoisomerase II cleavage sites [11, 18]. One of our patients had inv(16) AML and another had PML/RAR-α-positive APL. In one study where data on 48 patients with
<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Breast cancer therapy</th>
<th>Latency(^a)</th>
<th>Hematologic diagnosis</th>
<th>Cytogenetics</th>
<th>FISH</th>
<th>Initial therapy</th>
<th>Status at HSCT</th>
<th>HSCT conditioning</th>
<th>Graft</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>Epirubicin, cyclophosphamide (four cycles), docetaxel (three cycles); radiation</td>
<td>16 months</td>
<td>Pre B-ALL</td>
<td>47,XX, +X, t(4;11) (q21;q23)[20]</td>
<td>11q23/MLL positive = 94.2%</td>
<td>Hyper CVAD</td>
<td>CR</td>
<td>FTBI, etoposide</td>
<td>URD PBSC</td>
<td>Alive 35 months after ALL diagnosis; 31.8 months after HCT. No evidence of ALL</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>Doxorubicin, cyclophosphamide, docetaxel (four cycles); radiation</td>
<td>12 months</td>
<td>AML</td>
<td>52,XX, +6, +8, t[11;17] (q25;q25), +12, +18, +19,-20[17] /46,XX[4]</td>
<td>11q23/MLL positive = 73.1%</td>
<td>Induction: idarubicin + cytarabine (3 + 7), consolidation HiDAC (three cycles)</td>
<td>CR</td>
<td>TBI 2 Gy, fludarabine, ATG</td>
<td>Double URD UCB</td>
<td>Alive 36 months postdiagnosis of AML; 26.3 months after HCT. No evidence of AML</td>
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<tr>
<td>3</td>
<td>50</td>
<td>Doxorubicin, cyclophosphamide, 5-fluorouracil (six cycles)</td>
<td>12 months</td>
<td>MDS Int-1 risk</td>
<td>46, XX inv(11) q21q23 [6]/46,XX[14]</td>
<td>11q23/MLL positive = 5.9%</td>
<td>None</td>
<td>MDS</td>
<td>Busulfan, cyclophosphamide</td>
<td>MRD PBSC</td>
<td>Alive 31.8 months after diagnosis of MDS; 23 months after HCT. No evidence of AML</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>Doxorubicin, cyclophosphamide, 5-fluorouracil (six cycles)</td>
<td>38 months</td>
<td>Extramedullary AML with uterine involvement; no bone marrow involvement</td>
<td>Bone marrow: 46, XX[20]</td>
<td>(Uterine mass) 11q23/MLL = 85.3%</td>
<td>Induction: idarubicin + cytarabine (3 + 7), consolidation HiDAC (two cycles)</td>
<td>CR</td>
<td>Busulfan, etoposide</td>
<td>Auto PBSC</td>
<td>Alive 28 months after diagnosis of AML; 22.8 months after HCT. No evidence of AML</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
<td>Doxorubicin, cyclophosphamide, paclitaxel (four cycles); radiation</td>
<td>13 months</td>
<td>AML</td>
<td>Stemline: 46XX, der(11)del(11)(p11.2p13) t(11;19) q23p13.1, der(19)t(11;19) q23p13.1[14]/46.XX[6]</td>
<td>FISH positive for an MLL/ELL translocation</td>
<td>Induction: idarubicin + cytarabine (3 + 7), consolidation HiDAC (two cycles)</td>
<td>CR</td>
<td>Busulfan, cyclophosphamide</td>
<td>URD PBSC</td>
<td>Alive 26 months after diagnosis of AML; 20.4 months after HCT; no evidence of AML</td>
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<td>No.</td>
<td>Age</td>
<td>Breast cancer therapy</td>
<td>Latency</td>
<td>Hematologic diagnosis</td>
<td>Cytogenetics</td>
<td>FISH</td>
<td>Initial therapy</td>
<td>Status at HSCT</td>
<td>HSCT conditioning</td>
<td>Graft</td>
<td>Outcome</td>
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<tr>
<td>6</td>
<td>66</td>
<td>Doxorubicin, cyclophosphamide (four cycles), paclitaxel (four cycles); radiation</td>
<td>30 months</td>
<td>AML</td>
<td>46.XX.t(9;11) (p22q23)</td>
<td>Induction: arsenic trioxide + cytarabine (two cycles)</td>
<td>CR</td>
<td>Fludarabine, melphalan</td>
<td>URD PBSC</td>
<td>Alive 16 months after diagnosis of AML; 10.8 months after HSCT; no evidence of AML.</td>
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</tr>
<tr>
<td>7</td>
<td>56</td>
<td>Doxorubicin, cyclophosphamide (four cycles), taxotere (seven doses), cisplatin, gemcitabine; radiation</td>
<td>22 months</td>
<td>AML</td>
<td>46.XX, inv(16) (p13.122)[18]/47, idem, +8[4] 16q22/CBF positive = 67.6%</td>
<td>Induction: idarubicin + cytarabine (3 + 7)</td>
<td>CR</td>
<td>Fludarabine, melphalan</td>
<td>URD PBSC</td>
<td>Alive 22 months after diagnosis of AML; 20 months after HCT; relapsed 4.1 months post-HSCT. Reinduced into remission with 5-azacytidine and valproic acid. No current evidence of AML.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>Cyclophosphamide, doxorubicin, 5-fluorouracil (six cycles); radiation</td>
<td>AML leukemia cutis</td>
<td>46.XX.t(9;11) (p22q13) [11]/47.idem, +6[3]/46.XX[6] MLL positive = 19.5%</td>
<td>Induction: amsafide, cytarabine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Died of sepsis 25 days after start of chemotherapy; 1.5 months after diagnosis of AML.</td>
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<tr>
<td>9</td>
<td>45</td>
<td>Cyclophosphamide, methotrexate, 5-fluorouracil; radiation</td>
<td>APL</td>
<td>46.XX.add(10) (q22).ish ins(15;17) (q22q21.1q21.3) [20] RARA positive = 70.0%</td>
<td>Initial therapy: ATRA and idarubicin followed by maintenance with ATRA, 6-mercaptopurine and methotrexate</td>
<td>Morphologic and cytogenetic CR. MRD + by Q-PCR</td>
<td>Busulfan, cyclophosphamide</td>
<td>MRD PBSC</td>
<td>Alive 62 months after diagnosis of APL; 13.2 months after HSCT. No evidence of APL.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>Cyclophosphamide, methotrexate, 5-fluorouracil (three cycles); radiation</td>
<td>7 years 10 months</td>
<td>AML</td>
<td>46.XX[20] Not done</td>
<td>Induction: amsafide + cytarabine; consolidation: intermediate dose cytarabine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Relapsed after 3 months DOD</td>
<td></td>
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<tr>
<td>No.</td>
<td>Age</td>
<td>Breast cancer therapy</td>
<td>Latency*</td>
<td>Hematologic diagnosis</td>
<td>Cytogenetics</td>
<td>FISH</td>
<td>Initial therapy</td>
<td>Status at HSCT</td>
<td>HSCT conditioning</td>
<td>Graft</td>
<td>Outcome</td>
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</tr>
<tr>
<td>11</td>
<td>47</td>
<td>Adriamycin, cyclophosphamide, paclitaxel; radiation</td>
<td>9 months</td>
<td>AML FAB M5a</td>
<td>46,XX,add(5) (p15.3.1),t(8;16) (p11.2p13.3)[20]</td>
<td>Negative for MLL, RARA and CBF B</td>
<td>Induction: amonafide + cytarabine</td>
<td>Persistent disease (70% blasts, hypercellular marrow)</td>
<td>Busulfan, cyclophosphamide</td>
<td>MRD PBSC</td>
<td>Relapsed 2.4 months after HCT; DOD 74 days after HCT</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>Doxorubicin, cyclophosphamide (four cycles), paclitaxel (four cycles); radiation</td>
<td>9 months</td>
<td>AML</td>
<td>46,XX,t(9;11) (p11q23) [16]/46,XX[4]</td>
<td>MLL positive = 50.2%</td>
<td>Induction: clofarabine + cytarabine; consolidation: HiDAC (one cycle)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Relapsed after 3 months DOD</td>
</tr>
<tr>
<td>13</td>
<td>32</td>
<td>Cyclophosphamide, methotrexate, 5-fluorouracil (four cycles); radiation</td>
<td>6 years</td>
<td>AML</td>
<td>46,XX[20]</td>
<td></td>
<td></td>
<td>CR</td>
<td>Fludarabine, melphalan</td>
<td>MUD PBSC</td>
<td>Alive 67 months after diagnosis of AML; 53.3 months after HCT. No evidence of AML</td>
</tr>
<tr>
<td>14</td>
<td>50</td>
<td>Doxorubicin, cyclophosphamide (four cycles); radiation</td>
<td>24 months</td>
<td>AML</td>
<td>47,XX,+8,inv(8) (q11.2q22) x2,del(21) (q22)[20]</td>
<td></td>
<td>Induction: idarubicin + cytarabine; consolidation: HiDAC (three cycles)</td>
<td>CR</td>
<td>Fludarabine, melphalan</td>
<td>MRD PBSC</td>
<td>Alive 20 months after diagnosis of AML; 16 months after HSCT. No evidence of AML</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td>Doxorubicin, cyclophosphamide (four cycles); radiation</td>
<td>6 years</td>
<td>AML with aberrant lymphoid antigens</td>
<td>46,XX,t(9;22) (q34.1;q11.2)[8]/46,XX[8]</td>
<td>FISH = 11.8% BCR/ABL1+</td>
<td>Induction: idarubicin + cytarabine + imatinib; reinduction: HiDAC + imatinib</td>
<td>Persistent disease: 33% blasts, normocellular marrow</td>
<td>Busulfan, cyclophosphamide</td>
<td>MUD PBSC</td>
<td>Alive 10 months after diagnosis of AML; 4.4 months after HCT. No evidence of AML. Not on tyrosine kinase inhibitor</td>
</tr>
</tbody>
</table>

*Interval from beginning of chemotherapy.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; MDS, myelodysplastic syndrome; HiDAC, high-dose cytarabine; CR, complete remission; PBSC, peripheral blood stem cells; MRD, matched-related donor; MUD, matched-unrelated donor; UCB, umbilical cord blood; DOD, died of disease; NA, not applicable; MRD, minimal residual disease; Q-PCR, quantitative-PCR.
therapy-related leukemias/myelodysplasia carrying inv(16) and 41 patients with t(15;17) leukemia was analyzed, 33 patients had received treatment for breast cancer [10]. Similar to leukemia/myelodysplasia with an MLL abnormality, the latency period was short with median of only 22 months for inv(16) and 29 months for t(15;17). The majority of patients in that report had received therapy with topoisomerase II inhibitor and an alkylating agent. Interestingly, 10 patients with inv(16) and 12 patients with t(15;17) had received radiation therapy alone, thus demonstrating a role for radiotherapy as a possible causative agent in these chromosomal translocations. Similar to our patient with inv(16) who had trisomy 8 as well (case 7), additional chromosomal abnormalities were common in both inv(16) and t(15;17) groups, but had no impact on survival. Distinct pathologic features of therapy-related inv(16)-positive AML and APL have recently been described [9, 19].

The incidence of acute leukemia following adjuvant breast cancer treatment in general is low. In one report, the cumulative risk of developing secondary acute leukemia was 1.7% at 8 years after receiving an anthracycline-containing regimen [20]. As expected, the incidence is higher with regimens containing anthracyclines compared with nonanthracycline-containing regimens [20–22]. Dose-escalated anthracycline regimens appear to increase leukemia risk compared with standard dose anthracycline regimens [2, 20, 23–25]. An increased risk of AML/myelodysplastic syndrome (MDS) has been demonstrated in patients who have received support with colony-stimulating factors (granulocyte colony-stimulating factor or granulocyte macrophage-colony stimulating factor) during adjuvant chemotherapy [26, 27]. Whether use of these growth factors is an independent risk factor or simply a surrogate measure of the intensity of chemotherapy is presently unknown.

Limited evidence suggests that addition of taxane to an anthracycline-containing regimen increases leukemia risk [28, 29]. Seven of 15 patients in our series had received a taxane either with or following anthracycline chemotherapy. Radiation therapy for breast cancer is also associated with increased AML/myelodysplasia risk after adjusting for other treatment components [25, 26]. The factors that predispose individual patients to treatment-related AML/MDS remain unknown. One study showed an association of treatment-related leukemia with a polymorphism in the gene for CYP3A4 enzyme that metabolizes many chemotherapeutic agents [30]. The issue of genetic predisposition to therapy-related acute leukemia and myelodysplasia has been extensively reviewed recently [4, 31].

Our HSCT outcomes are superior to results of published studies of HSCT for therapy-related acute leukemia/MDS [32, 33]. For example, the 2-year disease-free survival for secondary AML as a whole was only 18 ± 11% in a retrospective analysis of registry data [32]. In our series, the majority of patients with acute leukemia were able to achieve CR before undergoing HSCT. This may explain the excellent HSCT results seen in this study as low disease burden at time of HSCT has been shown to be a favorable prognostic factor in other studies [32, 33]. In addition, most AML patients in this series had low-risk or intermediate-risk cytogenetics and it has been shown that after accounting for cytogenetics, patients with therapy-related AML or myelodysplasia have a similar allogeneic HSCT outcome to those with de novo disease [34]. It is also possible that patients who were potential candidates for HSCT were selectively referred to us thereby further improving our results. At our institution, the HSCT results of these patients do not appear to be inferior to that of patients with de novo AML/MDS. All but one patient in this series received nonradiation-based myeloablative conditioning for HSCT, which may account for the low transplant-related mortality. Since the majority of early-stage breast cancer patients receive locoregional radiation therapy, it may be preferable to avoid total body radiation-based myeloablative conditioning in these patients in order to minimize transplant-related mortality from cardiopulmonary toxicity. Our results would indicate that for acute leukemias with short latency period following adjuvant breast cancer therapy, a high rate of CR can be achieved after induction chemotherapy and the results of allogeneic HSCT are excellent when carried out in CR1 using a chemotherapy-conditioning regimen.

There is a need for precise assessment of leukemia/myelodysplasia risk with modern adjuvant chemotherapy regimens for breast cancer especially when treating patients whose risk of disease recurrence is low. Recent studies suggest that adjuvant chemotherapy regimens may require modulation based on pathologic features of the tumor. For example, among patients with node-positive disease, those who are HER2-negative and estrogen receptor-positive appear to gain little benefit from addition of paclitaxel to the chemotherapy regimen in at least one, retrospective, exploratory analysis [35]. In the future, genomic profiling may help identify low-risk patients who can be spared life-threatening complications such as acute leukemia/MDS resulting from adjuvant chemotherapy [36, 37].
references


7. Andersen MK, Christiansen DH, Kirchhoff M et al. Duplication or amplification of chromosome band 11q23, including the unrearranged MLL gene is a recurrent abnormality in therapy-related MDS and AML and is closely related to mutation of the TP53 gene and to previous therapy with alkylating agents. Genes Chromosomes Cancer 2001; 31: 33–41.


