Reduced-Intensity Allogeneic Stem Cell Transplantation for Co-Emergence of Chemotherapy-Refractory Follicular Lymphoma and Therapy-Related Myelodysplastic Syndrome

Yuji Shimura[a]   Junya Kuroda[a]   Nana Sasaki[a]   Hitoji Uchiyama[a, b]
Muneo Ohshiro[a, c]   Yayoi Matsumura[a, d]   Hisao Nagoshi[a]
Shinsuke Mizutani[a]   Tsutomu Kobayashi[a]   Yosuke Matsumoto[a]
Shigeo Horiike[a]   Masafumi Taniwaki[a]

[a]Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, [b]Division of Hematology, Department of Medicine, Kyoto Second Red Cross Hospital, and [c]Division of Hematology, Department of Medicine, Kyoto First Red Cross Hospital, Kyoto, and [d]Department of Hematology, Matsushita Memorial Hospital, Osaka, Japan

Key Words

Therapy-related myelodysplastic syndrome · Follicular lymphoma · Allogeneic transplantation

Abstract

A 54-year-old male was diagnosed with follicular lymphoma in September 2003. Despite multiple chemotherapies, including autologous hematopoietic stem cell transplantation (HSCT) with high-dose chemotherapy, the disease eventually relapsed. Additionally, bone marrow analysis revealed the co-emergence of therapy-related myelodysplastic syndrome (t-MDS) in February 2012. In March 2012, we performed related allogeneic HSCT for the treatment of both malignancies. This strategy was successful and the patient has remained free from both malignancies for 23 months. Allogeneic HSCT is a potent curative therapeutic option for both t-MDS and refractory follicular lymphoma.   © 2014 S. Karger AG, Basel

Yuji Shimura, MD, PhD
Division of Hematology and Oncology, Department of Medicine
Kyoto Prefectural University of Medicine
465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566 (Japan)
E-Mail yshimura@koto.kpu-m.ac.jp

KARGER

Introduction

Therapy-related myelodysplastic syndromes and acute myelogenous leukemia (t-MDS/AML) constitute the most serious late-onset complications caused by chemotherapy and/or radiotherapy. Recent advances in anticancer chemotherapy using various classical and novel anticancer agents have led to a higher rate of treatment success and longer survival for patients with cancerous diseases, including hematologic malignancies, so that the number of the so-called cancer survivors has increased during the past decade. This was also accompanied by an increase in the number of patients suffering from t-MDS/AML [1]. Because of chemorefractoriness due to frequent poor-risk cytogenetics and therapy-related organ damage caused by previous use of cytotoxic therapies, the treatment outcome for t-MDS/AML has remained dismal. The median survival for t-MDS/AML has been reported to be 6–8 months when treated by conventional chemotherapy, which is significantly shorter than that for de novo MDS and AML [2]. While allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapeutic strategy for t-MDA/AML, this strategy cannot be used for all patients due to the high frequency of therapy-related mortality [3, 4]. In particular, for patients exhibiting co-emergence of relapsed disease and t-MDS/AML, the life expectancy has been unfavorable due to the lack of a promising therapeutic modality [4].

The therapeutic outcome of non-Hodgkin lymphomas (NHLs) has been greatly improved over the past two decades as a result of the development of immunochemotherapy. While these advances in therapeutic strategies have greatly enhanced the cure rate for aggressive NHLs, such as diffuse large B-cell lymphoma, it remains difficult to achieve a cure for indolent lymphomas, such as follicular lymphoma (FL), even though survival has been prolonged. The repeated use of various kinds of immunochemotherapies over a long period has been generally required for patients with FL. The increase in anticancer agents and the longer survival period are associated with a higher occurrence rate of t-MDS/AML in FL [5]. Therefore, current and future topics regarding the treatment of FL include the therapeutic strategy for refractory/relapsed disease complicated by t-MDS/AML.

In this report, we describe the case of a patient with FL who relapsed after a series of treatments with a variety of chemotherapeutic agents. In addition, his condition was eventually complicated by the co-emergence of t-MDS.

Case Report

A 54-year-old male was admitted to hospital in September 2003 with systemic lymphadenopathy, fatigue and night sweating. Computed tomography scans confirmed cervical, axillary, mediastinal, para-aortic, mesenteric and inguinal lymphadenopathies. Laboratory tests showed an elevated soluble interleukin-2 receptor (14,800 U/ml) and elevated WBC (113.3×10^9/l), comprised of 89% of abnormal lymphoid cells. The bone marrow (BM) was also massively invaded by abnormal lymphoid cells. Biopsy of the cervical lymph node disclosed the diagnosis of FL grade 3A. In immunohistochemical examinations, lymphoma cells were positive for CD10, Bcl-2, and CD20, and t(14;18)(q32;q21) translocation was detected by fluorescence in situ hybridization. Eight cycles of R-CHOP consisting of rituximab, cyclophosphamide, adriamycin, vincristine and prednisolone and subsequent maintenance therapy with rituximab for 8 months induced complete remission (CR), but the disease relapsed 8 months after the cessation of rituximab. Salvage chemotherapy consisting of rituximab and fludarabine induced a partial response, but the disease relapsed again after 14 months. For the second salvage therapy, the patient was enrolled in a clinical trial for

Case Reports in **Oncology**

Case Rep Oncol 2014;7:188–194		190
DOI: 10.1159/000360905	© 2014 S. Karger AG, Basel www.karger.com/cro	

Shimura et al.: Reduced-Intensity Allogeneic Stem Cell Transplantation for Co-Emergence of Chemotherapy-Refractory Follicular Lymphoma and Therapy-Related Myelodysplastic Syndrome

treatment with everolimus, a new inhibitor of mammalian target of rapamycin. The drug induced CR, which sustained for 23 months, but lymphoma eventually relapsed (fig. 1a). A second biopsy of the cervical lymph node confirmed the diagnosis of relapsed FL without the evidence of transformation into a more aggressive lymphoma. Then, the patient underwent intensified chemotherapy using cyclophosphamide, high-dose Ara-C, dexamethasone, and etoposide (CHASE), radioimmunotherapy with ^{90}Y ibritumomab tiuxetan and myeloablative chemotherapy with melphalan, cyclophosphamide, etoposide, and dexamethasone (LEED) supported by autologous HSCT. The patient achieved CR, which was confirmed by ^{18}F-FDG-PET (PET) examination and BM analysis (no invasion and normal karyotype). However, 7 months after the transplantation, PET examination revealed generalized lymphadenopathy and uptake in the bilateral femoral nerve (suspected to be neurolymphomatosis). BM infiltration with abnormal lymphoid cells was also identified.

At this time, 81 months from the initial diagnosis of FL, we planned allogeneic HSCT using reduced-intensity conditioning (RIC). To reduce the tumor burden prior to RIC-HSCT, we administered three cycles of salvage therapy, comprised of rituximab and bendamustine, after which only minor cervical lymphadenopathy was identifiable by PET examination. However, myelosuppression accompanied by grade 4 neutropenia lasted for several weeks after the last dose of bendamustine, and BM analysis revealed hypocellularity with an increase in myeloblasts (5.2% of all nucleated cells) and multilineage dysplastic changes, which was documented in this case for the first time (fig. 2a). Chromosomal analysis revealed the presence of complex karyotypic abnormalities, including chromosome 7 deletion (fig. 2b). From these results, the diagnosis of t-MDS, refractory anemia with excess blasts-1, was made [6]. Regarding the MDS International Prognostic Scoring System, the patient was classified as intermediate-2 risk category [7]. Furthermore, the patient's condition was complicated by cytomegalovirus retinitis and required antiviral therapy for 4 weeks.

For simultaneous treatment of both chemotherapy-resistant FL and t-MDS, we performed RIC-HSCT with peripheral hematopoietic stem cells from his HLA-matched sibling (sister) 4 weeks after the diagnosis of t-MDS. At this time, the FL remained in partial remission. The conditioning regimen consisted of fludarabine (25 mg/m^2 × 5 days), melphalan (80 mg/m^2 × 1 day) and 4 Gy of total body irradiation (TBI). Cyclosporine A and short-term methotrexate were utilized as prophylaxis against graft-versus-host disease (GVHD). Neutrophil engraftment was confirmed on day 14 and platelet engraftment on day 22. There was no acute GVHD, and infectious complications, such as febrile neutropenia, *Clostridium difficile*-associated colitis, and reactivated cytomegalovirus retinitis, were treated successfully with antibiotics and antiviral agents. BM analysis on day 30 showed complete donor chimerism with a normal karyotype and without any myelodysplastic changes. The patient was discharged on day 56 and his condition was later complicated by chronic GVHD of the hepatic type that was alleviated successfully by re-dosing with cyclosporine A. PET examination on day 80 also showed no abnormal uptake (fig. 1b). Since then, CR of both FL and t-MDS has been maintained for 672 days at the timing of writing.

Discussion

According to the WHO classification, t-MDS is classified as one of the therapy-related myeloid neoplasms (t-MN) that can occur subsequent to exposure to cytotoxic agents or irradiation [6]. The latency period from first exposure to the development of t-MN varies by the dose intensity and the type of cytotoxic agents. For example, alkylating agents or

radiation therapies typically cause t-MDS 5–7 years after the exposure, and often manifest as complex chromosomal abnormalities, including monosomy 5 or 7. Topoisomerase II inhibitors are other leukemogenic agents that are potent inducers of t-AML, with 11q23 or 21q22 abnormalities occurring months to 3 years after the use. However, because most patients receive multiple drugs within the course of several years, it is difficult to determine the drug responsible for leukemogenesis in individuals [1, 6].

Fludarabine is a purine analog (antimetabolite) that is highly effective in the treatment of indolent malignant lymphoma or chronic lymphocytic leukemia. Fludarabine impairs DNA repair and induces cytopenia (lymphopenia), which can account for the increase of the incidence of secondary malignancy. Indeed, treatment with fludarabine, especially in combination with another cytotoxic drug, has been reported to increase the risk of t-MN [8]. High-dose chemotherapy supported by autologous HSCT may also contribute to the increased occurrence of t-MN [9]. In our case, various alkylating agents, topoisomerase II inhibitors and fludarabine were administered and high-dose chemotherapy was also administered within a short period. Thus, it is impossible to determine the drug or regimen responsible for the development of t-MDS.

Bendamustine is one of the promising cytotoxic agents among the alkylating agents that has been widely used for the treatment of indolent lymphoma. The drug has both alkylating and antimetabolite properties, and it has demonstrated significant efficacy for patients with indolent lymphoma [10]. Considering its mechanisms of action, bendamustine could be a more powerful inducer for the emergence of t-MN. However, there is no evidence for any relationship between administration of this drug and the development of leukemogenesis. We administered bendamustine 8 months after autologous HSCT, and the possible association between bendamustine and t-MDS could not be refuted in our case.

The therapeutic options for t-MDS/AML have been limited. Recently, the hypomethylating agents 5-azacitidine and decitabine have demonstrated equivalent efficacy for t-MDS and de novo MDS in terms of hematologic responses and have improved the overall survival for t-MDS. However, the overall survival for t-MDS still remains shorter than that for de novo MDS because of the poor preexisting risk factor, i.e., poor performance status, complex karyotypic abnormalities, or chemoresistance [11]. Thus, allogeneic RIC-HSCT is a potential curative treatment option. t-MDS patients who have received more than two chemotherapeutic regimens or have undergone allograft more than 6 months after the diagnosis showed a significantly higher nonrelapse mortality [3, 4]. Thus, an earlier decision for the choice of therapies with allogeneic HSCT is necessary, once the diagnosis of t-MDS is made.

FL is the most common indolent NHL of the germinal center B cells. Progress in immunochemotherapy using the anti-CD20 antibody rituximab combined with conventional and/or new cytotoxic agents, including bendamustine or fludarabine, has produced significant improvements in the response rate and survival [12–14]. However, most patients with FL eventually relapse and require subsequent therapies. The use of autologous or allogeneic HSCT for FL has not proven to have any significant survival advantage over chemotherapy alone [12]. However, for selected patients, especially those who relapse shortly after immunochemotherapy or those with histologic transformation to a more aggressive lymphoma, high-dose chemotherapy followed by autologous HSCT has prolonged the progression-free survival in cases of chemosensitive relapse [15]. Allogeneic HSCT holds promise for the cure of advanced stage FL, but has been associated with relatively high treatment-related mortality. Therefore, the indication of FL for allogeneic HSCT is further restricted and is generally considered at relapse after autologous HSCT. As a preparative regimen for allogeneic transplantation, RIC has been increasing because of its feasibility for elderly or heavily pretreated patients. Through retrospective analysis, prolonged overall

survival and lower treatment-related mortality have been reported with RIC for allogeneic HSCT. Thomson et al. [16] reported the outcome of related or unrelated allogeneic HSCT for FL with a conditioning regimen of fludarabine, melphalan, and alemtuzumab. With a median follow-up of 43 months, nonrelapse mortality and progression-free survival at 4 years were 15 and 76%, respectively.

Combing these, in our case with concurrent t-MDS and refractory FL, allogeneic HSCT was the only curative therapeutic strategy, despite the fact that the clinical outcome of allogeneic transplantation for patients with concurrent MDS and lymphoid malignancy remains quite unfavorable [17]. In our case, the less toxic RIC-HSCT from an HLA-matched sibling donor, the effective disease control of FL by bendamustine just before HSCT, and the short time between the diagnosis of t-MDS and allo-HSCT might all contribute to the success of the treatment.

Since there is no established common conditioning regimen that is effective for both malignant lymphoma and MDS, we used the RIC regimen, consisting of fludarabine, melphalan, and low-dose TBI, in consideration of the superior clinical results from Thomson et al. [16] and Yuji et al. [18]. In the previous reports and our experience, this regimen is most likely to be feasible and safe, even for the elderly or those who have previously received multiple chemotherapies, including high-dose chemotherapy, when efficacy sufficient to eradicate residual disease is warranted. The addition of TBI in the conditioning regimen might contribute to lowering the relapse rate [19].

In summary, t-MN is impairing instead of improving the clinical outcome with the advance of therapies for hematological malignancies. Therefore, the number of patients simultaneously suffering from t-MN and lymphoid malignancy will inevitably increase. Intervention with allogeneic HSCT should be considered as early as possible in such situations.

References

1   Leone G, Fianchi L, Voso MT: Therapy-related myeloid neoplasms. Curr Opin Oncol 2011;23:672–680.
2   Smith SM, Le Beau MM, Huo D, Karrison T, Sobecks RM, Anastasi J, Vardiman JW, Rowley JD, Larson RA: Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood 2003;102:43–52.
3   Spina F, Alessandrino PE, Milani R, Bonifazi F, Bernardi M, Luksch R, Fagioli F, Formica C, Farina L: Allogeneic stem cell transplantation in therapy-related acute myeloid leukemia and myelodysplastic syndromes: impact of patient characteristics and timing of transplant. Leuk Lymphoma 2012;53:96–102.
4   Litzow MR, Tarima S, Pérez WS, Bolwell BJ, Cairo MS, Camitta BM, Cutler CS, de Lima M, DiPersio JF, Gale RP, Keating A, Lazarus HM, Luger S, Marks DI, Maziarz RT, McCarthy PL, Pasquini MC, Phillips GL, Rizzo JD, Sierra J, Tallman MS, Weisdorf DJ: Allogeneic transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia. Blood 2010;115:1850–1857.
5   Morton LM, Dores GM, Tucker MA, Kim CJ, Onel K, Gilbert ES, Fraumeni JF, Curtis RE: Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975–2008. Blood 2013;121:2996–3004.
6   Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM, Hellstrom-Lindberg E, Tefferi A, Bloomfield CD: The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114:937–951.
7   Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Sanz M, Vallespi T, Hamblin T, Oscier D, Ohyashiki K, Toyama K, Aul C, Mufti G, Bennett J: International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079–2088.
8   Carney DA, Westerman DA, Tam CS, Milner A, Prince HM, Kenealy M, Wolf M, Januszewicz EH, Ritchie D, Came N, Seymour JF: Therapy-related myelodysplastic syndrome and acute myeloid leukemia following fludarabine combination chemotherapy. Leukemia 2010;24:2056–2062.
9   Tarella C, Passera R, Magni M, Benedetti F, Rossi A, Gueli A, Patti C, Parvis G, Ciceri F, Gallamini A, Cortelazzo S, Zoli V, Corradini P, Carobbio A, Mulé A, Bosa M, Barbui A, Di Nicola M, Sorio M, Caracciolo D, Gianni AM, Rambaldi A: Risk factors for the development of secondary malignancy after high-dose chemotherapy and

Shimura et al.: Reduced-Intensity Allogeneic Stem Cell Transplantation for Co-Emergence of Chemotherapy-Refractory Follicular Lymphoma and Therapy-Related Myelodysplastic Syndrome

autograft, with or without rituximab: a 20-year retrospective follow-up study in patients with lymphoma. J Clin Oncol 2011;29:814–824.

10 Cheson BD, Rummel MJ: Bendamustine: rebirth of an old drug. J Clin Oncol 2009;27:1492–1501.

11 Duong VH, Lancet JE, Alrawi E, Al-Ali NH, Perkins J, Field T, Epling-Burnette PK, Zhang L, List AF, Komrokji RS: Outcome of azacitidine treatment in patients with therapy-related myeloid neoplasms with assessment of prognostic risk stratification models. Leuk Res 2013;37:510–515.

12 Freedman A: Follicular lymphoma: 2012 update on diagnosis and management. Am J Hematol 2012;87:988–995.

13 Rummel MJ, Niederle N, Maschmeyer G, Banat GA, Grünhagen von U, Losem C, Kofahl-Krause D, Heil G, Welslau M, Balser C, Kaiser U, Weidmann E, Dürk H, Ballo H, Stauch M, Roller F, Barth J, Hoelzer D, Hinke A, Brugger W; Study group indolent Lymphomas (StiL): Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203–1210.

14 Tobinai K, Ishizawa K, Ogura M, Itoh K, Morishima Y, Ando K, Taniwaki M, Watanabe T, Yamamoto J, Uchida T, Nakata M, Terauchi T, Nawano S, Matsusako M, Hayashi M, Hotta T: Phase II study of oral fludarabine in combination with rituximab for relapsed indolent B-cell non-Hodgkin lymphoma. Cancer Sci 2009;100:1951–1956.

15 Montoto S, Corradini P, Dreyling M, Ghielmini M, Kimby E, López-Guillermo A, Mackinnon S, Marcus RE, Salles G, Schouten HC, Sureda A, Dreger P: Indications for hematopoietic stem cell transplantation in patients with follicular lymphoma: a consensus project of the EBMT-lymphoma working party. Haematologica 2013;98:1014–1021.

16 Thomson KJ, Morris EC, Milligan D, Parker AN, Hunter AE, Cook G, Bloor AJC, Clark F, Kazmi M, Linch DC, Chakraverty R, Peggs KS, Mackinnon S: T-cell-depleted reduced-intensity transplantation followed by donor leukocyte infusions to promote graft-versus-lymphoma activity results in excellent long-term survival in patients with multiply relapsed follicular lymphoma. J Clin Oncol 2010;28:3695–3700.

17 Zimmerman Z, Scott BL, Gopal AK, Sandmaier BM, Maloney DG, Deeg HJ: Allogeneic hematopoietic cell transplantation in patients with myelodysplastic syndrome and concurrent lymphoid malignancy. Bone Marrow Transplant 2012;47:804–809.

18 Yuji K, Miyakoshi S, Kato D, Miura Y, Myojo T, Murashige N, Kishi Y, Kobayashi K, Kusumi E, Narimatsu H, Hamaki T, Matsumura T, Kami M, Fukuda T, Masuo S, Masuoka K, Wake A, Ueyama J, Yoneyama A, Miyamoto K, Nagoshi H, Matsuzaki M, Morinaga S, Muto Y, Takeue Y, Taniguchi S: Reduced-intensity unrelated cord blood transplantation for patients with advanced malignant lymphoma. Biol Blood Marrow Transplant 2005;11:314–318.

19 Russell JA, Irish W, Balogh A, Chaudhry MA, Savoie ML, Turner AR, Larratt L, Storek J, Bahlis NJ, Brown CB, Quinlan D, Geddes M, Zacarias N, Daly A, Duggan P, Stewart DA: The addition of 400 cGY total body irradiation to a regimen incorporating once-daily intravenous busulfan, fludarabine, and antithymocyte globulin reduces relapse without affecting nonrelapse mortality in acute myelogenous leukemia. Biol Blood Marrow Transplant 2010;16:509–514.

Case Reports in **Oncology**

Case Rep Oncol 2014;7:188–194

DOI: 10.1159/000360905

© 2014 S. Karger AG, Basel
www.karger.com/cro

194

Shimura et al.: Reduced-Intensity Allogeneic Stem Cell Transplantation for Co-Emergence of Chemotherapy-Refractory Follicular Lymphoma and Therapy-Related Myelodysplastic Syndrome
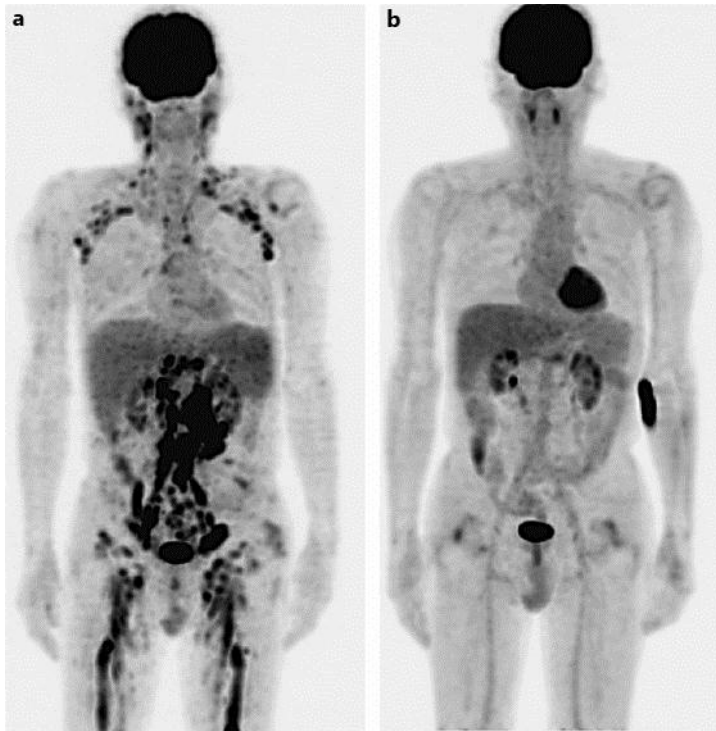
Fig. 1. ^{18}F-FDG-PET images at relapse (**a**) and 507 days after RIC-HSCT (**b**). Multiple indications of abnormal ^{18}F-FDG uptake (**a**) disappeared after RIC-HSCT.
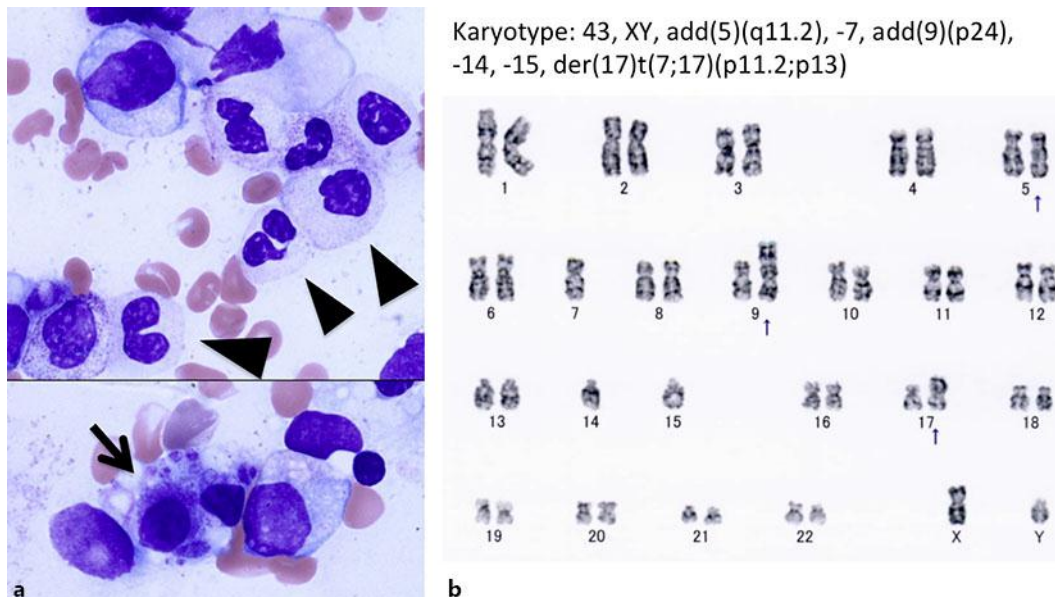
Fig. 2. Wright-Giemsa staining (**a**) and cytogenetic analysis (G banding) (**b**) of BM cells at the onset of t-MDS. Typical dysplastic hematopoietic cells, i.e., hypogranular neutrophils (arrowheads) and a micromegakaryocyte (arrow) were identified (**a**), and complex cytogenetic alterations, including chromosome 7 deletion, were detected (**b**).

KARGER