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

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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.

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

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 ($113.3 \times 10^9/l$), 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

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 ⁹⁰Y ibritumomab tiuxetan and myeloablative chemotherapy with melphalan, cyclophosphamide, etoposide, and dexamethasone (LEED) supported by autologous HSCT. The patient achieved CR, which was confirmed by ¹⁸F-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/m² × 5 days), melphalan (80 mg/m² × 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

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

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

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

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.

Combining 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.

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

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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).