Progressive Chronic Lymphocytic Leukemia After Allogeneic Hematopoietic Cell Transplantation

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Abstract
This case report presents a patient with poor-prognosis chronic lymphocytic leukemia (CLL) who was treated with chemotherapy and underwent allogeneic hematopoietic cell transplant (alloHCT) but ultimately progressed. The application of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL and the impact of alloHCT on secondary therapy for progressive CLL are discussed. (JNCCN 2012;10:1203–1206)

Case Report
A 62-year-old white man with an unremarkable medical history was diagnosed in 2008 with chronic lymphocytic leukemia (CLL) Rai stage 0 at an outlying hospital after a routine preoperative CBC revealed a lymphocytosis. The initial prognostic markers were equivocal with positive Zap-70 expression but negative CD38 expression. The patient was observed without treatment. After 6 months, the patient developed progressive lymphadenopathy, weight loss, anemia, and thrombocytopenia. Subsequently, he received treatment with rituximab and fludarabine (FR) × 6 cycles and experienced a partial response. Six months later, he developed progressive lymphadenopathy and worsening anemia and thrombocytopenia. He was referred to the authors’ institution for further treatment. Cytogenetic evaluation revealed mutation of p53, del(13q), and del(11q). Because of the high-risk features of his disease, an allogeneic hematopoietic cell transplant (alloHCT) was planned and a donor search initiated. In the interim he received salvage chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) × 6 cycles and rituximab and bendamustine (BR) × 3 cycles. He experienced a poor response to both regimens, with progressive lymphadenopathy on CT scan and persistent involvement of the bone marrow.

The patient proceeded to alloHCT with residual disease. He received a matched unrelated donor alloHCT conditioned with fludarabine, melphalan, and total body irradiation. Acute graft-versus-host disease (GVHD) prophylaxis consisted of low-dose methotrexate, tacrolimus, and mycophenolate mofetil (MMF). Neutrophil and platelet engraftment occurred on day 12 and 18 after transplantation, respectively. Bone marrow mixed chimerism on day 30 after transplantation was 45% to 49% donor. All immunosuppression with MMF and tacrolimus was rapidly tapered off to encourage conversion to donor chimerism and any nascent graft-versus-leukemia effect. On day 46, the patient developed new painful cervical lymphadenopathy. Progressive disease was confirmed on restaging CT scan. Shortly thereafter, the patient developed liver function test elevation. The total bilirubin was 5.3 mg/dL, aspartate aminotransferase was 265 IU/L, alanine aminotransferase was 165 IU/L, and alkaline phosphatase was 1001 IU/L. Cytomegalovirus DNA copy number was negative on PCR. A liver biopsy was performed to differentiate liver GVHD from CLL involvement and was consistent with CLL. One cycle of dexamethasone, high-dose cytarabine, and carboplatin (DHAC) was given with little effect and replaced with alemtuzumab. Alemtuzumab was given at a total dose of 450 mg divided over 15 doses and well tolerated. On day 110,
the bone marrow was hypocellular, mixed chimerism was 100% donor, and flow cytometry was negative for CLL. The patient’s lymphadenopathy had also regressed and his disease was restaged as a complete response.

The patient continued to have liver function test elevation and occult liver acute GVHD was suspected in addition to the previously shown graft-versus-leukemia (GVL) effect against his CLL in the liver. The total bilirubin peaked at 27.3. Punch biopsy of an erythematous rash was consistent with acute GVHD of the skin. Alemtuzumab given at 10 mg subcutaneously was initiated once a week for liver GVHD. The patient also received methylprednisolone at 1 mg/kg, which was later tapered to oral prednisone, tacrolimus, and beclomethasone. Bone marrow mixed chimerism on day 150 was 100% donor with 40% to 65% cellularity and no flow cytometry evidence for CLL (Figure 1). Despite initial improvement, the patient’s liver function worsened and he developed hepatic encephalopathy, with repeat liver biopsy revealing nonspecific cholestasis. The patient’s overall condition worsened and he succumbed at day 169 posttransplantation.

Discussion

CLL is the most common leukemia in the North America and Europe, with an age-adjusted incidence of 4.2 per 100,000 persons per year. One in 202 men and women will develop CLL during their lifetime. It is characterized by the progressive accumulation of lymphocytes in the peripheral blood, bone marrow, and lymphoid tissues. It is diagnosed on flow cytometry through the identification of the CD5+CD20+CD23+ immunophenotype. At diagnosis, 25% to 50% of patients will be asymptomatic, with abnormalities detected only with routine blood work. The Rai and Binet systems are widely used in clinical practice to stage disease but do not predict disease progression or response to therapy. Rather, the heterogeneous clinical course of CLL can be prognosticated with the presence of an unmutated immunoglobulin heavy chain V region (IgHV), greater than 30% CD38+ cells, greater than 20% ZAP-70–positive cells, or the del(11q) and del(17p) (including p53 mutation) cytogenetic abnormalities. All of these markers are associated with poor prognosis. The del(17p) cytogenetic abnormality is found in 7% of patients with CLL, often in association

Figure 1. Bone marrow (BM) involvement with chronic lymphocytic lymphoma (CLL) is inversely related to donor chimerism, showing the graft-versus-leukemia effect. CLL is in remission while BM showed 100% donor allele. BMT, bone marrow transplant.
with unmutated IgHV, and confers the worst prognosis. Favorable risk factors include del(13q) and a lymphocyte doubling time that is greater than a year. The CLL section of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Hodgkin’s Lymphoma recommends risk-adapted therapy based on cytogenetic abnormalities (available online at NCCN.org). Therefore, cytogenetic and fluorescence in situ hybridization analyses must be obtained before initiating therapy. Initial treatment with chemotherapy is recommended for patients with del(17p) or del(11q); p53 mutation is encompassed by del(17p). Patients without these cytogenetic abnormalities are only treated if they have significant disease-related symptoms, potential end-organ dysfunction, or progressive lymphadenopathy, anemia, or thrombocytopenia. Because clonal evolution can occur during treatment, repeat cytogenetic analysis should be performed between changes in therapy or if the disease course suddenly changes so that therapy can be redirected. AlloHCT can potentially cure CLL because of GVL effects. Non-myeloablative conditioning followed by alloHCT results in a 4- to 5-year progression-free survival rates of 42% to 39%, respectively, and overall survival rates of 65% to 50%, respectively, in patients with high-risk CLL, indicating the long-term efficacy of alloHCT in this disease and supporting the existence of a GVL effect. AlloHCT should be offered to any eligible patient with del(17p) who is in complete or partial remission, those with del(11q) who experience a partial remission, and those without del(17p) or del(11q) who experience a poor response to second-line therapies. The timing of transplant is crucial, and adequate time should be allowed to identify a suitable donor. Clinicians should be careful not to lose the window of opportunity for transplant afforded by clinically controlled CLL.

After an initial period of observation, the patient was treated with FR, R-CHOP, and finally BR in rapid succession. Despite a 90% overall response and 47% complete response rate for FR, an overall response rate of 71.5% for R-CHOP, and a 45.5% response rate for BR in patients with fludarabine-refractory CLL, this patient continued to have progressive disease. His clinical course was consistent with his high-risk cytogenetic features, which predicted for resistance to conventional therapy. Alemtuzumab has been shown to be beneficial in therapy-refractory CLL. However, because this patient had bulky extensive lymphadenopathy, chemotherapy was given because of its potentially greater cyto-reductive effects. Altogether, these chemotherapy regimens produced a partial response.

This patient underwent alloHCT but soon experienced relapse. NCCN Guidelines suggest treatment in a clinical trial or with second-line therapy for relapsed or refractory disease after alloHCT. DHAC was initially given for cytoreduction. Because of reports indicating decreased effects in bulky disease, alemtuzumab was not initially given, although it was started after the poor response to DHAC. Surprisingly, a greater-than-expected effect was seen and the patient experienced a complete remission.

Alemtuzumab is a recombinant humanized IgG1 monoclonal antibody directed against human CD52. It has clinical activity in patients with CLL, including those with mutated p53, although it has decreased efficacy in bulky lymphadenopathy greater than 5 cm, with only 58.8% lymph node reduction. The authors hypothesize that the greater-than-expected effect was from the presence of a new immune system from the donor. Prospective studies of the kinetics of CLL minimal residual disease after alloHCT have shown that GVL effects can be modulated by donor lymphocyte infusions and withdrawal of immunosuppression. Furthermore, T-cell donor chimerism greater than 95% by day 30 after alloHCT has been shown to predict for sustained molecular remission in CLL at 1 year. The combination of withdrawing immunosuppression and giving alemtuzumab may have facilitated conversion to full donor chimerism and subsequent GVL effects eradicating the CLL. Neutrophils and natural killer cells have also been shown to be instrumental to the antitumor activity of alemtuzumab. Polymorphisms in immunoglobulin Fc receptors FcγR2a and FcγR3a, which result in stronger binding to the IgG1 Fc region, have also been shown to enhance antibody-dependent cell-mediated cytotoxicity for many antibodies in clinical use, such as rituximab, cetuximab, and trastuzumab. All of these are potentially different compared with the patient’s germline status after alloHCT, and could explain the greater-than-expected effect observed for alemtuzumab. In this patient, alemtuzumab was also used for its anti-GVHD activity in addition to its antitumor activity. Thus, the history of alloHCT should be obtained before initiating therapy.
loHCT considerably affected the selection of therapeutics for treatment of relapsed/refractory CLL.

Conclusions
NCCN Guidelines for CLL recommend a risk-adapted approach to therapy based on cytogenetic analysis with alloHCT for patients with refractory disease or poor prognostic markers. As shown in this case report, cytogenetic analysis is crucial for planning therapy. Additionally, the use of alloHCT introduces new considerations when selecting continued therapy for refractory or relapsed disease. Many therapies, especially immune-based therapies such as alemtuzumab that were less ineffective before alloHCT, may find newly increased efficacy in the presence of a new immune system and new uses specific to alloHCT.

References