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Successful treatment with allogeneic bone marrow transplantation of an early relapse of ALK-positive anaplastic large cell lymphoma

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Anaplastic large cell lymphoma, (ALCL) first described by Stein et al. in 1985,[1] is a high-grade lymphoma, accounting for 10% of childhood lymphomas. It is characterized by a proliferation of CD30-positive large lymphoid cells with pleomorphic nuclei and single or multiple prominent nucleoli. Lineage-specific antigens show a T-cell or null-cell phenotype.[2,3] In approximately 60% of ALCL, ALK expression can be detected by immunohistochemistry. The expression of ALK is due to chromosomal translocations involving the ALK gene and different partner genes.[4-7] The translocation t(2;5)(p23;q35) is found in up to 75% of ALK + ALCL, resulting in the NPM-ALK chimeric protein.[8,9] ALK-positive ALCL occurs predominantly in children and young adults. It has a broad morphological spectrum and different morphological variants have been described.[10] Up to 80% of pediatric patients with ALCL can be cured with multi-agent chemotherapeutic regimens. Patients who suffer a relapse have an 85% chance of achieving a second complete remission, but 40% of them will have a second relapse. Disease free survival (DFS) at 3 years after the first relapse was reported to be 28% for patients with early relapse (<12 months after first diagnosis) versus 68% for patients with late relapse (>12 months after diagnosis). Second and further relapses occur in both groups. Patients resistant to chemotherapy or suffering from early relapse have a poor prognosis.[11,12] Autologous SCT (ASCT) seems to have a place in the treatment of patients with ALCL as consolidation therapy or in patients who achieved a second complete remission, but prospective studies are needed to confirm the advantage of ASCT versus conventional chemotherapy.[12] Allogeneic HSCT has been proposed as therapeutic option in patients with relapse of ALCL.[13] Clinical reports of such patients are rare, only two children were described who received allogeneic bone marrow transplantation and who remain in complete remission 56 and 40 months after the transplant (14). We report the clinical history, therapy and outcome after allogeneic HSCT of a girl with early relapse of ALCL.

Case report

An 8 year-old girl presented in March 2003 with high fever, skin rash, hepatosplenomegaly and enlargement of the lymph nodes. Computer tomography showed pathological lymph nodes bilateral in the neck, mediastinum, mesenterium and retroperitoneum. Histological examination of biopsies from a cervical lymph node and a skin lesion led to the diagnosis of ALCL. Bone marrow (BM) trephine biopsies, examination of cerebrospinal liquid and Tc99 bone scan were negative. Histological and immunohistochemical studies showed the presence of T-cell marker CD3 and typical markers for ALCL: CD30, EMA and ALK. Karyotyping of the tumor cells demonstrated the presence of the t(2;5) translocation.

According to the St. Jude classification, this girl had a stage III ALCL. Informed consent was obtained and she was enrolled in the European ALCL-99 high-risk study (Table 1). There was a prompt clinical response to therapy and a complete evaluation performed after 3 cycles of chemotherapy could not reveal residual tumor. At admission for the fourth course, she presented with fever and chemotherapy was delayed for one week. Soon a relapse became evident, with clinical enlargement of lymph nodes and reappearance of skin lesions. Relapse of ALCL was histologically confirmed. Staging examinations showed again mediastinal and abdominal tumor masses. BM and central nervous system examination was negative for tumor cells.

Reinduction treatment was given according to a protocol draft of the EICNHL (European Intergroup co-operation on Childhood Non-Hodgkin-Lymphoma) for patients with relapse of ALCL (Table 2).

After the first reinduction course, immediate clinical response was seen and an allogeneic hematopoietic stem cell transplantation (HSCT) with a matched unrelated donor (MUD) was scheduled, since there was no sibling donor available. A few days before the start of the conditioning regimen a fast growing cervical mass was indicative for second relapse. The lymph node regressed after one injection of vincristin and corticosteroids for 3 days. The patient then received the planned conditioning regimen.

Preparative therapy consisted of Thiotepa (10 mg/kg) at day-7, VP16 (40 mg/kg) at day - 6 and TBI (12 Gy total dose in 2×2 Gy fractions/day) at days - 4, - 3, - 2. A total of 6×10^8/kg nuclear cells were infused with CD34+ fraction of $4{,}6\times10^6$/kg. Medications to prevent graft versus host disease (GvHD) were ATG (14 mg/kg), Cyclosporine A and Methotrexate (3×10mg/m^2). The MUD-HSCT was well tolerated, engraftment of white blood cells was seen at day +26, platelets engraftment occurred at day + 23. Because the patient had no signs of GvHD, CsA was tapered off and stopped on day +120. Complete evaluation of tumor parameters and imaging studies performed 3, 6, 9 and 12 months after HSCT showed no signs of residual masses. DNA examination of blood and bone marrow demonstrated full donor chimerism.

For this child, with a well-documented early relapse of ALK+ ALCL, a MUD-HSCT was the last option of cure. Now, more than 18 months after MUD-HSCT, she remains in continuous complete remission (CR). She is going to school again and enjoying a very good quality of life. There are no signs of GvHD and until now no transplant- related complications have occurred.

Discussion

This child with an early relapse of ALK+ ALCL, has remained in remission after matched unrelated stem cell transplant for more than one year, with full donor chimerism. Autologous stem cell transplantation is efficacious in some patients with relapse of ALCL, but second relapses after high dose therapy are not a rare event. Brugières et al. reported second relapse in 5 out of 15 patients transplanted in CR2 at a median time of 16 months, all three patients who underwent autologous ASCT in partial remission died from disease progression within 10 months, whereas 2 out of 3 patients treated in CR3 relapsed again.[11] The role of allogeneic HSCT remains to be determined.

We postulate that in our patient a graft versus lymphoma (GvL) effect might play a role in the sustained remission after allogeneic HSCT. In accordance with this hypothesis Verdonck et al. reported favorable outcomes after allogeneic HSCT in patients with resistant and recurrent low-grade lymphomas.[15] It is well known that there is a higher incidence of lymphomas in AIDS patients and in patients with other immune deficiencies.[16] These observations indicate that the immune system plays a pivotal role in the pathogenesis of such malignancies. Our patient did not develop GvHD, but GVL can occur in the absence of clinical GVHD.[17,18]

Conclusion

Allogeneic HSCT might be a valid option in the treatment of patients with early relapse of ALCL. As second and subsequent relapses occur after autologous stem cell transplantation in ALCL, we hypothesize that a graft versus lymphoma effect effect and not only the high-dose chemotherapy might explain the sustained complete remission in this case, even when no signs of GvHD are present. Prolonged follow-up and more patients are needed to determine the benefits of allogeneic stem cell transplantation in patients with resistant disease or early relapse of ALCL.

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References

1. Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, et al. The expression of the Hodgkins-disease associated antigen Ki-1 in reactive and neoplastic lymphoid-tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood, 66: 848, 1985.
2. Delsol G, Al Saati T, Gatter C, Gerdes J, Schwarting R, Caveriviere P, et al. Coexpression of epithelial membrane antigen (EMA), Ki-1 and interleukin-2 receptor by anaplastic large cell lymphomas: diagnostic value in so-called malignant histiocytosis. Am J Pathol, 130: 59, 1988.
3. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JKC, Cleary ML, et al. A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood, 84: 1361, 1994.
4. Foss H, Anagnostopoulos I, Araujo I, Assaf C, Demel G, Kummer J, et al. Anaplastic large-cell lymphomas of T-cell and null-cell phenotype express cytotoxic molecules. Blood, 88: 4005, 1996.
5. Rimokh R, Magaud JP, Berger F, Samarut J, Coiffier B, Germain D, et al. A translocation involving a specific breakpoint (q35) on chromosome 5 is characteristic of anaplastic large cell lymphoma (Ki-1 lymphoma). British Journal of Haematology, 71: 31, 1989.
6. Mason D, Bastard C, Rimokh R, Dastugue N, Huret J, Kristoffersson U, et al CD30-positive large cell lymphomas ('Ki-1 lymphoma') are associated with a chromosomal translocation involving 5q35. British Journal of Haematology, 74: 161, 1990.
7. Lamant L, Meggetto F, Al Saati T, Brugieres L, de Paillerets B, Dastugue N, et al. High incidence of the t(2;5)(p23;q35) translocation in anaplastic large cell lymphoma and its lack of detection in Hodgkin's disease. Comparison of cytogenetic analysis, reverse transcriptase-polymerase chain reaction and P-80 immunostaining. Blood, 87: 284, 1996.
8. Shiota M, Fujimoto J, Takenaga M, Satoh H, Ichinohasama R, Abe M, et al. Diagnosis of t(2;5)(p23;q35)-associated Ki-1 Lymphoma with immunohistochemistry. Blood, 84: 3648, 1994.
9. Shiota M, Nakamura S, Ichinohasama R, Abe M, Akagi T, Takeshita M, et al. Anaplastic large cell lymphomas expressing the novel chimeric protein P80 (NPM/ALK): a distinct clinopathological entity. Blood, 86: 1954, 1995.
10. Jaffe ES, Harris NL, Stein H, Vardiman JW. (Eds.): World Health Organization Classification of Tumors. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press, 2001:230-235.
11 Brugières L, Quartier P, Le Deley MC, Pacquement H, Perel Y, Bergeron C, et al. Relapses of childhood anaplastic large-cell lymphoma: Treatment results in a series of 41 children - A report from the French Society of Pediatric Oncology. Ann Oncol., 11: 53, 2000.
12. Fanin R, Ruiz de Elvira MC, Sperotto A, Baccarani M, Goldstone A. Autologous stem cell transplantation for T and null cell CD30-positive anaplastic large cell lymphoma: analysis of 64 adult and paediatric cases reported to the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant, 23: 437, 1999.
13. Liso A, Tiacci E, Binazzi R, Pulford K, Benedetti R, Carotti A, et al. Haploidentical peripheral-blood stem-cell transplantation for ALK-positive anaplastic large-cell lymphoma. The Lancet Oncol., 5: 127, 2004.
14. Chakravarti V, Kamani NR, Bayever E, Lange B, Herzog P, Sanders JE et al. Bone-marrow transplantation for childhood Ki-1 lymphoma. J Clin Oncol., 8: 657, 1990.
15. Verdonck LF, Dekker AW, Lokhorst HM, Petersen EJ, Nieuwenhuis HK. Allogeneic versus autologous bone marrow transplantation for refractory and recurrent low-grade non-Hodgkin's lymphoma. Blood, 90: 4201, 1997.
16. Levine A. Lymphoma complicating immunodeficiency disorders. Ann Oncol., 5: S29-S35, 1994.
17. MacKinnon S, Papadopoulos EB, Carabasi MH, Reich L, Collins NH, Boulad F, et al. Adoptive immunotherapy evaluating escalating doses of donor leukocytes for relapse of chronic myeloid-leukemia after bone-marrow transplantation: separation of graft-versus leukemia responses from graft-versus- host disease. Blood, 86: 1261, 1995.
18. Barret AJ, Mavroudis D, Tisdale J, Molldrem J, Clave E, Dunbar C, et al. T cell-depleted bone marrow transplantation and delayed T cell add-back to control acute GVHD and conserve a graft-versus-leukemia effect. Bone Marrow Transplant, 21: 543, 1998.*E-mail: victoria.bordon@belgacom.net*