The paper describes a rare case of secondary acute myeloid leukemia that occurred after double autologous hematopoietic stem cell transplantation (AHSCT) for non-Hodgkin's lymphoma (NHL). A 46-year-old female was admitted to hospital in June 2000 with a prior history of progressive weakness. On physical examination a general lymphadenopathy and hepatosplenomegaly were present. The diagnosis of peripheral T-cell non-Hodgkin's lymphoma was made upon the histological examination of the node taken from her neck. The clinical stage was determined as IVB (Ann-Arbor). The patient started chemotherapy with CHOP regimen and after 6 cycles she achieved a complete remission (CR). The first autologous bone marrow transplantation (ABMT) was performed in December 2000 using CBV conditioning. The first relapse occurred two months later and the patient was administered CHOP twice and three cycles of CHOP with bleomycin with CR2 in May 2001. The second autologous peripheral blood stem cell transplantation (APBSCT) was performed in September 2001, after stem cell mobilization with IVE regimen. Conditioning consisted of total body irradiation (TBI) and cyclophosphamide. One year later a second relapse occurred with a general lymphadenopathy and enlargement of lymph nodes in mediastinum. She achieved CR3 in June 2003 after chemotherapy with CMOP and vinblastine with prednisone. In September 2003 her overall condition worsened and the total white cell count increased. She was diagnosed as having acute myeloid leukemia (AML). The patient did not respond to chemotherapy and died of myocardial infarction in October 2003. On autopsy there was no evidence of lymphoma.

Key words: acute leukemia, autologous transplantation, non-Hodgkin's lymphoma.

Secondary acute myeloid leukemia after double autologous hematopoietic stem cell transplantation for peripheral T-cell non-Hodgkin's lymphoma: a case report

Przypadek wtórnej, ostrej białaczki szpikowej u pacjentki po dwukrotnie wykonanym autologicznym przeszczepieniu hemopoetycznych komórek macierzystych z powodu chłoniaka z obwodowych limfocytów T

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Introduction

Therapy-related acute myeloid leukemia (t-AML) after either conventional-dose regimens or high-dose chemotherapy (HD) followed by autologous hematopoietic stem cell transplantation (AHSCT) for non-Hodgkin's lymphoma (NHL) is an important problem. The risk of t-AML is varied and it is thought to be higher after HD-AHSCT as compared to the risk after standard therapy [1].

Case report

A 46-year-old female was admitted to our hospital in June 2000 because of a 2-month history of increasing weakness and night sweats. On physical examination a general lymphadenopathy and hepatosplenomegaly were present. Ultrasonography revealed enlarged lymph nodes in the abdomen. The chest X-ray was normal. The histopathological examination of a node surgically taken from her neck revealed peripheral T-cell NHL. Bone marrow was occupied by lymphoma cells in 50%. The white blood cell count (WBC) was elevated – 23.7 x 10^9/l with 80% of segmented neutrophils in differential. The biochemical tests were normal except for lactate dehydrogenase (LDH – 555 IU). The clinical stage was determined as IV and IPI was 3. A combination chemotherapy was started and after 6 cycles of CHOP, the patient achieved a complete remission (CR). The first autologous bone marrow transplantation (ABMT) was performed in December 2000 using carmustine (BCNU), cyclophosphamide (CTX) and etoposide (VP-16) (CBV regimen for consolidation). The bone marrow was harvested after G-CSF administration for 3 days at 0.9 mg. CR remained for 3 months. The first relapse occurred in February 2001, with lymph node involvement at primary localization. The WBC count was elevated with predominance of mature neutrophils. Bone marrow was disease-free. The patient was given cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP 2x) and CHOP with bleomycin (3x) with CR2 in May 2001. The second autologous peripheral blood stem cell transplantation (PBSCT) was performed in September 2001, after stem cell mobilization with ifosfamide, etoposide and epirubicin (IVE regimen). Conditioning consisted of total body irradiation (TBI)

W pracy opisano rzadki przypadek wtórnej, ostrej białaczki szpikowej u pacjentki po 2-krotnie wykonanym zabiegu autologicznego przeszczepienia hemopoetycznych komórek macierzystych z powodu chłoniaka nieziarniczego. 46-letnia chora została przyjęta do szpitala w czerwcu 2000 r. z powodu postępującego osłabienia. W badaniu fizykalnym stwierdzono uogólnioną limfadenopatię oraz hepatosplenomegalię. Rozpoznanie chłoniaka nieziarniczego z obwodowych komórek T postawiono na podstawie badania histologicznego węzła chłonnego szyjnego. Stadium kliniczne choroby ustalono na IVB wg klasyfikacji Ann-Arbor. Chora otrzymała leczenie cytostatyczne CHOP i po 6 cyklach uzyskano stan całkowitej remisji choroby. W grudniu 2000 r. wykonano pierwszą autotransplantację szpiku kostnego stosując kondycjonowanie CBV. Nawrót choroby wystąpił 2 mies. później. Pacjentka uzyskała kolejną remisję w maju 2001 r. po 2-krotnym leczeniu CHOP i 3 cyklach CHOP z bleomycyną.
Druga transplantacja z obwodowych komórek macierzystych została wykonana we wrześniu 2001 r., po wcześniejszej mobilizacji komórek macierzystych programem IVE. Kondycjonowanie obejmowało naświetlanie całego ciała oraz cyklofosfamid. Kolejny nawrót schorzenia pod postacią uogólnionej limfadenopatii i masy węzłowej w śródpiersiu miał miejsce rok później. Kolejną, trzecią remisję udało się uzyskać po leczeniu schematami CMOP oraz winblastyną z deksametazonem. We wrześniu 2003 r. stan chorej uległ znacznemu pogorszeniu, w badaniu morfologii krwi zaobserwowano narastanie leukocytozy. Przeprowadzono dodatkową diagnostykę rozpoznając ostrą białaczkę szpikową. Pomimo zastosowanego intensywnego leczenia cytostatycznego, chora zmarła w październiku 2003 r., a przyczyną śmierci był zawał mięśnia sercowego. W badaniu autopsyjnym nie stwierdzono cech chłoniaka.

Słowa kluczowe: ostra białaczka, przeszczep autologiczny, chłoniak nieziarniczy.

and cyclophosphamide. One year later a second relapse occurred with a general lymphadenopathy and enlargement of lymph nodes in mediastinum. The WBC count was again markedly increased but this time the immature granulocytic cells (promyelocytes and myelocytes) were present. The cytogenetic analysis did not reveal chromosome Philadelphia. BCR/ABL oncogene was negative. She was administered cyclophosphamide, mitoxantrone, vincristine and prednisone (CMOP 4x) and vinblastine with prednisone (5x) with CR3 in June 2003. Three months later the patient was referred to our hospital in a poor general condition, with fever up to 40 degrees and clinical symptoms of pneumonia. There were no enlarged lymph nodes. The WBC count varied from 108 up to 300 x 10^9/l with 70% of myelomonoblasts. Surface-marker immunophenotyping of the leukemia cells showed positive results for CD13, CD15, CD33, CD34, CD117, CD133 and HLA-DR. There were no metaphases and chromosomal analysis could not be performed. Taking into consideration the results obtained from cytological and cytochemical exams and the expression of antigens on leukemic cells, we diagnosed AML (M4 FAB). She did not respond to chemotherapy and died of myocardial infarction in October 2003. On autopsy there was no evidence of lymphoma.

Discussion

Therapy-related AML is usually resistant to chemotherapy and has a very poor prognosis [1]. Up to 10% of NHL patients treated with either conventional-dose chemotherapy or HD-AHSCT may develop secondary malignancies within 10 years [2]. The median time from AHSCT to onset of t-AML is reported to be 31 to 44 months [3], but in almost 30% of patients that period is shorter and malignancy occurs within 12 months or earlier [1]. An analysis performed by Krishnan et al. on 612 patients with NHL who had undergone HD-AHSCT revealed priming with etoposide for stem cell collection to be associated with an increased risk of t-AML [4]. Most studies underscore the influence of high-dose alkylating agents and topoisomerase II inhibitors on the occurrence of secondary malignancies. An increased risk of developing t-AML is also found for conditioning with total body irradiation at doses 13.2 Grey [5].

The total doses of chemotherapeutic agents given to our patient were as follows: cyclophosphamide – 30400 mg, ifosfamide – 30000 mg, etoposide – 5000 mg, doxorubicin – 1000 mg, vincristine – 30 mg, bleomycin – 45 mg, mitoxantrone – 80 mg, vinblastine – 120 mg, cytarabine – 680 mg and carmustine – 700 mg. Accumulation of high-dose etoposide together with alkylating drugs, TBI used as conditioning and age of over 40 years at the time of AHSCT might be related to the onset of secondary AML in that case. It was proven that exposure to topoisomerase II inhibitors is associated with monocytic (M4 and M5) phenotype of acute leukemia. It is also likely that growth-factor therapy used routinely in our patient may facilitate the selection of aberrant progenitors [4, 6].

Taking into consideration the whole disease course we noticed that the elevated WBC count (varied between 20 and 30 x 10^9/l) persisted during the whole observation. It dropped after chemotherapy and then it was gradually increasing, being elevated before the next cycle. At diagnosis we noted the prevalence of segmented cells, but then the increased proportion of immature granulocytes was present in peripheral blood and bone marrow. We assume it may reflect an abnormal immune response that is due to a variety of cytokines as it was described for Hodgkin's lymphoma [7]. The coexistence of lymphoma with chronic neutrophilic leukemia is less likely.

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