Acute Myeloblastic Leukemia: Difficulties of Treatment, Complications and Evolution

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Introduction: This paper presents a special case of an acute myeloblastic leukemia accidentally diagnosed on a 57 years old asymptomatic person without occupational exposure, without a medical history, with normal blood count, without thrombocytopenia, as a result of routine hematological tests that reveal the presence of more than 10% blasts on peripheral blood smear.

Material and method: Bone marrow aspirate revealed 80% blasts and flow cytometry confirmed the diagnosis of acute myeloblastic leukemia LAM0. Cytogenetic examination showed normal karyotype 46, XX. The treatment aims to induce, maintain and consolidate remission. Since the classical therapeutic approach with Idarubicine and Cytarabine 3+7 was not tolerated, adjustments were necessary to 2+5, four courses being administered. During the remission period Methotrexate and Purinotel maintenance treatment was administered, it was obtained a tolerable quality of life, the patient resumed his work. The first relapse occurred after approximately one year. Later medical courses were established after chemotherapy protocol with Clofarabine and Cytarabine, but after intolerance, neutropenia, sepsis and death occurred.

Results: Because of the severe prognosis and infectious complications the treatment was difficult and dose adjustments were necessary according to patient’s tolerance. Bone marrow transplant was not possible due to the lack of a compatible family donor.

Conclusions: This case of acute myelogenous leukemia treatment reflects the difficulties and complications occurred during the disease evolution. However remission periods with a tolerable quality of life were obtained, duration of treatment was approximately three years until death.

Keywords: AML, complications, evolution

Introduction

Acute myeloid leukemia (AML) is a clonal disease of non-lymphoid hematopoietic stem cells characterized by their neoplastic aberrant proliferation, with blocking differentiation and maturation processes in the earliest stages of development and accumulation of immature cells, myeloblast cells. Leukemia has been recognized as a disease in 1845 by Virchow while in 1875 Friedreich describes the acute evolution of the disease. The causes of this disease are not known, though it have been recognized as predisposing conditions exposure to radiation, chemical agents and viruses, constitutional chromosomal abnormalities and smoking. It is the commonest acute leukemia in adults. In AML symptoms and physical examination are non-specific [1,2]. Morphological appearance of cellular elements allows classifying acute myeloid leukemia by morphological FAB classification. The WHO classification correlates the morphological, genetic and clinical features to categorize cases of AML into unique clinical and biological subgroups. Immunophenotyping allow the study of monoclonal antibodies to cell surface antigens which differentiate AML from ALL and confirm the diagnosis of M0, M6 and M7 [3]. Cytogenetic analysis detects translocations and deletions that provide independent prognostic information in AML. The treatment of AML comprises two main phases: remission induction therapy and post remission therapy which includes consolidation therapy and maintenance therapy. During each phase chemotherapy is given. The aim of the chemotherapy is to eliminate the leukemic cells and achieve complete hematological remission, defined as normal bone marrow cellularity, blast cells <5%, normalization of peripheral blood count with no blast cells, neutrophils ≥1.5 × 10⁹/L, platelets ≥100 × 10⁹/L and Hb >10 g/dL [4].

Case presentation

This paper presents a special case of an acute myeloblastic leukemia accidentally diagnosed on a 57 years old asymptomatic person without occupational exposure, without a medical history, with normal blood count without thrombocytopenia, as a result of routine hematological tests that reveal the presence of more than 10% blasts on peripheral blood smears (Figure 1). This outcome raised the suspicion of an acute leukemia. The patient is sent by general practitioner to the hematology department for further investigation and diagnosis. Physical examination showed lightheadedness, without peripheral adenopathy. Laboratory data were within normal limits WBC 9130/mm³, Hb 11.2 g/dl, Htc 34.2%, Plt 211,000/mm³. Besides routine hematological tests to determine the paraclinical status, special examinations were performed. These examinations included bone marrow aspirate, flow cytometry and cytogenetic analysis. Bone marrow aspirate showed 80% blasts. Flow cytometry revealed 64% blasts with antigenic profile: CD 13+ (92.71%), CD 33+ (39.6%), CD 15+ (54.91%), CD 11c+ (38.24%), CD 34+ (99.4%), CD
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38+ (96.58%), HLA-DR + (99.5%), CD 117+ (99.6%), CD 123+ (65.33%), CD 7+ (98%) (Figure 2). This result confirmed the diagnosis of acute myeloid leukemia, immature form, AMLo. Cytogenetic analysis was performed on bone marrow which was processed by the indirect method. 15 metaphases were directly examined of which 5 were hypodiploidie. The karyotype was 43,XX,-7,-9,-19[5]/46,XX[10]. Analysis that focused on infection status were also performed: HBs Ag negative, Anti HBc 0.076 (reactivity 0–1) positive, Anti HBc-IgM negative, Hbe Ag negative, Anti HBe 0.564 (reactivity <1) positive, Anti-CMV IgM negative, Anti-CMV IgG positive. Mycologica and bacteriological examination, pharyngeal exudate and urine culture were negative. Thus the first course of induction with Idarubicin and Cytarabine was initiated. Since the classic Idarubicin and Cytarabine 3+7 approache was not tolerated by the patient, dose adjustments were necessary in 2+5 regimen evolution being favourable. After this treatment a febrile granulocytopenia with sepsis, anemia and secondary thrombocytopenia occurred. Biological status showed WBC 70/mm3, Hb 8.4 g/dl, Htc 24.6%, Plt 51,000/mm3. Physical examination revealed perianal fistula and local hyperemia. To stimulate hematopoiesis, granulocyte growth factors, Neupogen was given. Also the treatment included prophylactic therapy with broad-spectrum antibiotics, antifungal and antiviral drugs. Anemia was corrected with transfusions of whole blood and packed red blood cells, and thrombocytopenia with transfusions of platelets. Evolution being favorable after about 12 days the second induction course with Cytarabine and Idarubicin 2+5. This was followed by a new episode of febrile granulocytopenia with sepsis, lab data showing WBC 470/mm3, Hb 8.4 g/dl, Htc 24.6%, Plt 17,000/mm3. This required a new treatment with granulocyte growth factors, broad-spectrum antibiotics, antifungal drugs, transfusions of whole blood, packed red blood cells and platelet. Thus were given four courses of induction with Cytarabine and Idarubicin 2+5, followed by episodes of febrile granulocytopenia, anemia and thrombocytopenia. Patient had asthenia, weakness, pale skin, purpura and petechiae on the legs. Control flow cytometry: immunophenotyping of bone marrow emphasized 0.25 myeloblasts CD 34+/CD 15+. The fourth induction course was followed by sepsis, the infection with Escherichia coli being confirmed by hemoculture. After treatment, the evolution was slowly favorable being followed by a remission period on which the patient obtained a tolerable quality of life and managed to resume the daily activities. The patient has not tolerated high doses of Cytarabine due to the repeated episodes of sepsis. Sepsis states were caused by the following germs: Escherichia coli, Pseudomonas aeruginosa. Because of intolerance after getting his first remission, maintenance therapy with Methotrexate and Purinetol was given. The first relapse occurred after approximately one year after diagnosis. Patient had fever, asthenia, weakness, pale skin, purpura, petechiae, skin infiltration, bone pain. Bone marrow aspirates and flow cytometry showed 8% blasts. The result of repeated cytogenetic examination was 46, XX[27]/47,XXX[2] karyotype, meaning that two of the 29 examined metaphase presented X monosomy. Karyotype change shows an unfavorable evolution and the possibility of resistance to chemotherapy. Two reinduction courses of chemotherapy in adjusted doses of Cytarabine and Mitoxantrone led to a favorable evolution. The treatment included broad-spectrum antibiotics, antifungal, antiviral drugs and immunoglobulin. After a remission period for about nine months a reactivation of the disease with secondary granulocytopenia, anemia, thrombocytopenia and oral mycosis occured. Laboratory investigations showed WBC 1580/mm3, Hb 10 g/dl, Htc 29.4%, Plt 44,000/mm3 and mycological examination on the tongue, Candida. Cytogenetic analysis did not reveal numerical or structural chromosomal abnormalities resulting normal karyotype 46, XX. Flow cytometry: immunophenotyping of bone mar-
row showed 29% blasts with antigenic profile: CD 33+ (40%), CD 13+ (68.7%), CD 64+ (65.76%), HLA-DR+, CD 7+, CD 15+, CD 34+, CD 117+, CD 11c+ (63.64%), CD 123+ (86.42%). Therefore chemotherapy with Cytarabine and Mitoxantrone was resumed. Prevention of the infection was done with broad-spectrum antibiotics, antiviral and antifungal drugs. Clinical and hematological evolution was slowly favorable. The patient continued chemotherapy with Etoposide and Cytarabine, presenting bone marrow aplasia after the treatment. In aplasia stage was administered granulocyte growth factors, antibiotics, platelet concentrate. After about 6 months of remission period, the patient is hospitalized with general malaise, weakness, fatigue, pale skin and mucus jaundice. Paraclinical status highlighted WBC 140/mm³, Hb 9.8 g/dl, Htc 29.1%, Plt 21,000/mm³, SGOT 21U/l, SGPT 76U/l, GGT 119 U/l, TBIL 2.82 mg/dl and myological examination Candida glabrata. Flow cytometry on bone marrow immunophenotyping showed 7–8% blasts with antigenic profile: CD 33+, CD 13+, CD 64+, HLA-DR+, CD 7+, CD 15+, CD 34+, CD 117+, CD 11c+, CD 123+. It has been found reactivation of the disease and a new cytostatic course with Cytarabine and Mitoxantrone treatment is given. This was followed by a posttreatment febrile granulocytopenia. As a result granulocyte growth factors, broad spectrum antibiotics, antiviral, antifungal and hepatoprotective due to cytolyosis were administrated. Anemia and thrombocytopenia were treated by packed red blood cells and platelet transfusions and electrolytic disturbances by administration of electrolyte solutions. It was later given a new cytostatic course with Etoposide and Cytarabine, followed by secondary severe granulocytopenia, secondary anemia and thrombocytopenia and oral mycosis. After about two months of treatment the disease becomes active being confirmed by bone marrow aspirate result which showed 87% blasts. It is established a new chemotherapy course with Etoposide, Cytarabine and Idarubicin which is interrupted due to bone marrow aplasia. Granulocyte growth factors, broad spectrum antibiotics, antivirals, antifungals, platelet transfusions, red blood cells and electrolyte solutions were administrated. It is given a new regimen using CLARA protocol in three courses with Cytarabine and Clofarabine known as “salvage therapy”. Unfortunately after the first course the general state of the patient got worse and neutropenic fever occurred leading to sepsis which was fatal. The patient did not have comorbidities but after induction courses he had repeated episodes of sepsis due to the very impaired immune status.

**Results**

It was successfully obtained the administration of four induction therapy courses with Idarubicin and Cytarabine after 2+5 protocol because the classical therapeutic approach 3+7 was not tolerated by the patient. These were followed by febrile granulocytopenia, anemia and secondary thrombocytopenia episodes. Granulocytopenia was treated with granulocyte growth factors. Anemia was corrected with whole blood transfusions and packed red blood cells and thrombocytopenia with platelet transfusion. Electrolyte disturbances were treated by administration of electrolyte solutions. Remission was achieved over a period of seven months, during which the patient resumes its daily activities, within acceptable limits. At first relapse patient received two induction chemotherapy courses with adapted doses of Mitoxantrone and Cytarabine. After a remission for about nine months the reactivation of the disease is assessed and the reinduction chemotherapy consisting of two courses with Cytarabine and Mitoxantrone alternating with other two courses with Etoposide and Cytarabine were administered. One year later a new reactivation of the disease is found. This was associated with cytogenetic abnormalities Polychimiotherapy with Etoposide, Cytarabine and Idarubicin was given but later was interrupted due to bone marrow aplasia. Because of bone marrow relapse a course of “salvage therapy” after the CLARA protocol with Clofarabine and Cytarabine was attempted. Then a febrile neutropenia occurred with sepsis that lead to death. Although without comorbidities the patient had repeated episodes of sepsis due to the very impaired immune status. Bone marrow transplantation was not possible due to the lack of a compatible family donor. The patient was proposed for allotransplant from an unrelated donor from a foreign centre but unfortunately the patient died before the approval of the transplant.

**Discussions**

Generally the management of older patient with AML is a difficult challenge because of comorbidities which can limit treatment options. This disease tends to be more aggressive biologically and the outcomes are worse than in young patient [5]. The difficulties of this case were due to immature form of acute myeloid leukemia, the poor prognosis, treatment intolerance which required adapted dose and changes in treatment schedule [6,7,8]. The post-treatment infectious complications with granulocytopenia were frequent. Disease progression was fluctuating, with relapse, though with favorable clinical and hematological evolution considering the fact that in the remission periods the patient had a tolerable quality of life and work resumed. Based on the recommendations of the Medical Research Council (MRC) AML 10 Trial regarding the karyotype changes, the patients are included into three cytogenetic risk groups: favorable, intermediate and severe. In compliance with this classification the patient had an intermediate cytogenetic risk [9]. According to SWOG (Southwest Oncology Group) criteria there have been defined four cytogenetic risk categories. In low-risk category with favorable prognosis are included patients with inv(16)/t(16;16)/del(16q) or t(15;17) with additional anomalies: t(8;21) without del(9q) or without being part of a complex karyotype. Intermediate risk category includes patients with +8, -Y, +6, del(12p) or normal karyotype. High category with
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severe prognosis is defined by the presence of one or more anomalies: inv(3q)/t(3;3), -5/del(5q), -7/del(7q), del(9q), t(6;9), t(9;22) and of complex karyotypes. The unknown risk category includes all other chromosomal changes [10]. All chromosomal abnormalities of the unknown SWOG prognosis are placed in intermediate risk group of Medical Research Council (MRC) AML 10 Trial classification. Based on SWOG (Southwest Oncology Group) criteria the patient was included in unknown cytogenetic risk group. After 3 years of treatment a relapse occurred with marked fatigue, fever, bleeding syndrome with purpura, petechiae, bone pain, intolerance to treatment with general malaise, febrile neutropenia sepsis and death.

Conclusions
This case of acute myeloid leukemia, the immature form, Mo FAB, reflects the treatment difficulties and complications during this disease evolution. The complexity of treatment was due to frequent infectious episodes which made difficult to obtain outcomes. Although the prognosis was severe because of the morphological form with repeated relapses and short remissions, karyotype changes during evolution, it has managed to obtain during periods of remission a tolerable quality of life, survival time being approximately 3 years from diagnosis.

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References