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Personalized Management of Chronic Myeloid Leukemia Presenting with Ovarian Apoplexy and Review of Health Emergency Cases

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Abstract

Introduction: Chronic myeloid leukemia (CML) may significantly affect quality of life and life expectancy in the accelerated and acute phases, especially if presented with health emergencies. **Objective:** The purpose of the study was the evaluation of the personalized management milestones in CML cases presented with ovarian apoplexy and the analysis of the international experience on health emergencies in this leukemia. **Materials and Methods:** An original, case-report study was performed. The diagnosis was confirmed by cytological, cytogenetic and molecular examinations of the peripheral blood and bone marrow at the comprehensive research cancer center—Institute of Oncology from Moldova. The real-time PCR was performed for quantitative detection of BCR-ABL gene p210 and p190 transcripts. The ECOG Scale and complete hematologic response (CR) estimated the short-term results. The ECOG performance status served as a measure of functional status. Its scores range from 0 to 5 and correlate with the level of patient functioning. CR is the disappearance of all detectable clinical and hematological signs of malignant neoplasm in response to treatment. CR span was assessed in months. The overall and relapse-free survivals asserted the long-term results of treatment, and were evaluated in months as a case. **Results:** CML may be manifested by life-threatening conditions, including infections and thrombotic events, splenic infarcts and ruptures, bleedings, etc. CML with the uncommon onset under the form of the ovarian apoplexy is described. The hematological CR was obtained under the treatment with imatinib mesylate. The molecular CR and the long-lasting overall survival (197.5 months) were achieved after the treatment with nilotinib. Under the treatment with tyrosine kinase inhibitors, the patient did not experience the disease burden and side effects, and resumed her work, with a good life quality (ECOG score is 0).

Discussion: CML may be manifested by life-threatening health emergencies, especially thrombotic events, splenic infarcts and ruptures, bleedings, etc. The CML patients with high leukocyte and platelet counts may experience also different symptoms of hyperviscosity: tinnitus, priapism, stupor, visual abnormalities and cerebrovascular accidents. However, the management of CML with the life-threatening conditions, especially in the accelerated and acute phases, should be realized with participation of the multidisciplinary teams. **Conclusions:** The ovarian apoplexy may serve as a presenting feature of CML in young females with a highly elevated leukocyte count. The reported CML case underwent successful personalized management with 2 generations of tyrosine kinase inhibitors, even if designated with Socal intermediate-risk score and complicated by a health emergency.

Keywords

Leukemia, BCR-ABL Gene Transcripts, Health Emergencies, Ovarian Apoplexy, Tyrosine Kinase Inhibitors, Survival

1. Introduction

Chronic myeloid leukemia (CML) is registered in up to 20% of all cases with leukemias in adults and emerges from a clonal malignant myeloproliferation of the stem cell [1] [2] [3] [4] [5]. This hematological malignancy develops mostly in a working-age population with the age of 40 - 55 years. The total number of CML patients grew annually by 2% between the years 2007-2016, and the total number of deaths declined annually by 1% during the years 2008-2017. Higher morbidity by CML was observed among persons exposed to radiation in high doses, including the survivors of the atomic blasts in Japan, Ukraine and patients undergoing radiotherapy, and in those with obesity [6] [7] [8]. The course of this leukemia comprises 3 succeeding phases: chronic, acceleration and acute, and each of them may be associated with the life-threatening emergencies, including the ovarian apoplexy as a presenting feature [4] [5] [9] [10] [11] [12] [13]. The patients with advanced phases and relapses of CML may manifest a sizable disease burden and negative effect on their life quality, working productivity and daily living activities, especially if complicated with health emergencies. The unusual cases of CML were reported in the literature, which evolved into the medical emergencies and required a multidisciplinary approach. Arulkumaran S. et al were among the first, who provided a detailed description of a female patient presented to the gynecological unit as a case of septic abortion [14]. The history and clinical examination suggested the occurrence of double pathology of septic abortion and CML. The histological investigation of the tissues removed from the uterus detected leukemic infiltrates. The diagnosis of CML was proved by the bone marrow aspiration and biopsy. Most careful clinical and laboratory examinations, thus, helped in diagnosisand appropriate treatment of CML presented

as a gynecological emergency. The purpose of our study was the evaluation of the personalized management milestones in CML cases presented with the ovarian apoplexy and the analysis of the international experience on health emergencies in this leukemia.

2. Materials and Methods

Herewith, we evaluated the management milestones in CML case presented with the ovarian apoplexy and reviewed the literature concerning the health emergencies in CML. The patient follow-up was related to the in-patient and ambulatory care. The type of hematological malignancy was identified according to the International Revised 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues [15] [16]. The diagnosis was confirmed by cytological, cytogenetic and molecular examinations of the peripheral blood and bone marrow [1] [3] [5] [7] [10] [12] [13] [17]. The real-time PCR with the usage of sequence-specific DNA probes was performed for quantitative detection of p210 and p190 transcripts of BCR-ABL fusion gene while proceeding with CML diagnosis. The bone marrow cytogenetic and molecular analyses were accomplished every 6 - 12 months until the complete cytogenetic remission was achieved, and annually thereafter [1] [13] [16] [17]. Main outcome measures [18]: The ECOG Scale and complete hematologic response (CR) estimated the short-term results. The ECOG performance status served as a measure of functional status. Its scores range from 0 to 5 and correlate with the level of patient functioning. CR is the disappearance of all detectable clinical and hematological signs of malignant neoplasm in response to treatment. CR span was assessed in months. The overall and relapse-free survivals asserted the long-term results of treatment [18], and were evaluated in months as a case. The whole research protocol for CML studies was approved by the Research Ethic Board of the State University of Medicine and Pharmacy "N. Testemitanu". The informed consent was obtained from the patient to assure the researcher and Research Ethic Board that the participant knows every aspect of participation in the study.

3. Results

The CML patient has been followed up and treated from 2006 to 2022 at the Institute of Oncology in the hematology and outpatient departments. This patient was a 21-year-old female, initially hospitalized in the hematology department in June 2006 with the left upper abdominal discomfort and fatigue. She denied fever and any weight loss. During the interrogation the patient mentioned the rough onset of the disease on 8th of June 2006, with the intensive pain in the projected zone of the left ovary. The same day this patient was admitted to the National Research and Practical Emergency Medicine Center with the diagnosis of left-sided ovarian apoplexy. The suturation of the left ovary was performed. The following clinical and laboratory findings were revealed: splenomegaly, anemia (Hb 85 g/L) and elevated leukocyte count (165.0×10^9/L) with the shift

to the left. These suggestive findings served the indication for an appointment at hematologist from the Institute of Oncology. On June 23 clinical examination showed mild anemic syndrome, moderate splenomegaly (palpable at the level of +1 cm below the costal arch) and minor hepatomegaly. The spleen and liver surfaces were smooth and painless at palpation. Peripheral and intraabdominal lymph nodes weren't enlarged at palpation. Cardiovascular, respiratory and nephrourinary systems proved without abnormal findings. ECOG performance score was 2. Complete blood count identified the following changes at the time of diagnosis: hemoglobin 85 g/l, erythrocytes 3.4×10^{12}/L, leukocytes 430.0×10^{9}/L, platelets 510.0×10^{9}/L, erythrocyte sedimentation rate 4 mm/h, blasts 9%, promyelocytes 8%, myelocytes 33%, metamyelocytes 12%, band neutrophils 16%, segmented neutrophils 8%, eosinophils 2%, basophils 2%, monocytes 8%, lymphocytes 7%. Bone marrow aspiration revealed the increased cellularity, myeloid hyperplasia (84.0%), and normal percentage of blast cells (1.0%). Cytogenetic analysis and real-time quantitative PCR of the bone marrow cells detected 100% and 42% expression of Ph-chromosome and BCR-ABL p210 transcript, respectively. BCR-ABL p210 transcript subtype was b3a2. BCR-ABL p190 transcript proved to be negative. Biochemical test detected the slightly elevated lactate dehydrogenase value—297 U/L. Thus, the diagnosis of late chronic phase of CML was confirmed. Socal prognostic score was 1.16, placing this patient into the intermediate-risk group. The ultrasound scanning of the abdomen found moderate splenomegaly (length = 16 cm) and insignificant hepatomegaly, regional lymph node enlargement.

The patient underwent single-agent cytoreduction therapy with hydroxyurea 3000 mg daily, with the achievement of partial hematological remission. Since 2007 she underwent the targeted therapy with imatinib mesylate at a daily dosage of 400 mg, with the achievement of complete hematological remission and minor cytogenetic remission in December 2008 (Ph-chromosome = 60%). ECOG performance score was recovered up to 0. Due to the persistence of Ph chromosome and BCR-ABL p210 transcript in the bone marrow cells, the daily dosage of imatinib mesylate was boosted up to 600 mg. In December 2009 the follow-up cytogenetic analysis of the bone marrow cells did not detect Ph-chromosome. The follow-up real-time quantitative PCR proved a major/optimal molecular response in January 2014: BCR-ABL p210 transcript was 0.03%. The patient continued targeted therapy with imatinib mesylate at a daily dose of 600 mg, followed by nilotinib at a daily dose of 600 mg due to the persistence of BCR-ABL p210 transcript. The repeated real-time quantitative PCR didn't reveal BCR-ABL p210 transcript under the therapy with nilotinib. Thus, the complete molecular remission was achieved. By January 2022, the overall survival accounted 197.5 months, and the relapse-free survival—154.5 months. Under the treatment with tyrosine kinase inhibitors, the patient did not experiencethe disease burden and side effects, and resumed her work, with a good life quality (ECOG score is 0). The reversal of the unfavorable medical and social patterns of

CML improved the individual productivity and could be considered as an optimizing factor of patients' management.

4. Discussion

The narrative review of the bibliographic sources was fulfilled in the form of a synthesis. The accumulation of information for this study was performed by analyzing the data from the specialized international references and official statistics concerning CML. The scientific publications were searched over the Google Search, PubMed, NCIB, Medscape, Z-library, and Hinari database, by the keywords: "chronic myeloid leukemia", "incidence", "health emergencies", "ovarian apoplexy", "BCR-ABL gene transcripts", "diagnosis", "management", "treatment", "molecular response", "survival", "prognosis". We studied more than 50 bibliographic reference sources in order to accomplish the Discussion section. Twenty-eight essential primary sources were determined and selected, according to the relevance of the impact score.

CML may be manifested by the life-threatening health emergencies, especially thrombotic events, splenic infarcts and ruptures, bleedings (after dentistry procedures, epistaxis, cerebral), etc. [5] [9] [19]. The CML patients with high leukocyte and platelet counts also may experience different symptoms of hyperviscosity: tinnitus, priapism, stupor, visual abnormalities and cerebrovascular accidents [4] [5].

Leukemias associated with spontaneous hemoperitoneum are the uncommon events and generally involve leukemic cell infiltration of female genital tract [20]. CML, other leukemias and lymphomas may affect genital tract but there is a scarcity of literature pertaining to leukemia resulting in corpus luteal cyst rupture leading to hemoperitoneum without histopathological involvement of female genital tract with leukemic cells. Ovarian cyst hemorrhage in CML patient had been first reported by Valentsik in 1951 [21]. Chaudhar *et al.* reported a 32-year-old, multiparous female who presented with hypovolemic shock with hemoperitoneum, splenomegaly, and was subsequently diagnosed with a chronic myeloproliferative disorder [20]. The splenic hemorrhage was initially thought to be the cause of hemoperitoneum but an ultrasound scan proved corpus luteal hemorrhage as the etiological cause. Emergency ultrasonography and Doppler scan revealed hemoperitoneum and splenomegaly without any site of rupture. An empty normal sized uterus with echogenic lesion (3.8 × 2.7 cm) in left ovary suggestive of corpus luteal cyst was observed. Thus, the final diagnosis of corpus luteal hemorrhage with myelo-proliferative neoplasm was made. Conservative management was successful thereby averting surgery. Patient was started on imatinib after diagnosis of CML was established by real-time PCR test of the peripheral blood RNA. She conceived while on treatment and delivered a healthy newborn with her disease being under remission.

Another case report of 39 years old female, who presented with the evidence of intra-abdominal bleeding to the emergency department of the University

Hospital of North Midlands (UK), proved to be related to CML [22]. An urgent CT-scan revealed a massive intra-abdominal hematoma with the suggestion of a gynecological origin. The patient was then transferred immediately to the operating theatre where she had an emergency laparoscopy to evacuate the hematoma and identify the source of bleeding. In view of persistently elevated leukocyte (54.8×10^9/L) and platelet (695.0×10^9/L) counts, a multidisciplinary team of gynecologists, general surgeons and hematologists decided to perform a bone marrow biopsy under the care of the hematology team. The biopsy and real-time PCR revealed BCR/ABL1 re-arrangement, strongly suggestive of a Philadelphia chromosome, typically associated with CML. This article highlighted the critical role of Multi-Disciplinary Team involvement in elaborating management plans to achieve the best possible outcomes for those patients.

In 2008 Joseph D.E. and Durosinmi M.A. performed an attempt to describe the non-reversal neurological deficiencies complicating CML [23]. Patients' case folders and hematological malignancies register of CML cases followed-up in Jos University Teaching Hospital between 1995 and 2005 were retrospectively studied. Thirty-three cases of CML had been seen within the study period. Five (15.15%) of them had one or more sensori-neural defects. Fundoscopy revealed leukemic depositions on the retina. The authors reported about the regression of the hyperleucocytosis-induced complications under the conventional therapy. Nevertheless, the complications due to other pathogenetic mechanisms such as leukemic depositions did not recovered to their pre-morbid condition followed disease control despite the usage of the accessible contemporary treatment programs.

CML initial presentations, thus, were considered as the extramedullary myeloid blast crises involving the central nervous system and multiple lymph nodes, with no findings of the acceleration phase or blast crisis in the peripheral blood or bone marrow [24]. Although the induction therapy was not consolidated with allogeneic stem cell transplantation, the complete cytogenetic and molecular remission was maintained under a single-agent therapy with dasatinib for 3.5 years since the diagnosis with no evidence of the active extramedullary disease. The authors suggested that dasatinib might play an important role in controlling not only chronic phase of CML, but also its extramedullary central nervous system blast crisis, especially when combined with whole-brain radiation therapy.

CML is known to trigger nephrotic syndrome. A case of CML patient with nephrotic syndrome was reported by Yoshizaki N *et al.* in 1989 [25]. The renal biopsy with histological examination revealed membranous proliferative glomerulonephritis. Other published case reports also established an association between nephrotic syndrome and CML. The histology of the renal biopsies was either minimal change disease or membranous glomerulonephritis. Nephrotic syndrome is a well-recognized documented complication after allogeneic peripheral stem cell transplantation [26]. It commonly emerges due to the autoimmune glomerulonephritis and is supposed to be a clinical sign of the graft versus host disease. The authors analyzed several case reports of nephrotic syndrome occurring after the peripheral stem cell transplantation. Most of those cases were

membranous nephropathy. Other pathologic conditions were due to the diffused proliferative glomerulonephritis and minimal change disease. All of the cases had concomitant findings of the graft versus host disease, either acute or chronic. The authors suggested that graft versus host disease in those cases generated an autoimmune response, thereby triggering immune-complex deposition in the glomeruli.

Priapism is a complication uncommonly observed in leukemia [27] [28]. Nevertheless, about 20% of all priapism cases are related to hematological diseases. The incidence of priapism in adult leukemic patients is about 1% - 5%. Leukemia is commonly manifested by painful priapism. Four different mechanisms were described: sludging of leukemic cells in the corpora cavernosa and the dorsal veins of penis; venous congestion of the corpora cavernosa due to the mechanical pressure on the abdominal veins by massive splenomegaly; infiltration of the sacral nerves with leukemic cells; leukemic proliferation in the central nervous system. The following case characterized priapism as an uncommon manifestation of CML. A 21-year-old male with a steady painful erection of penis for 19 hours at home was reported in the medical literature. The patient underwent immediate irrigation and decompression of priapism by urologist at the emergency department. This approach led to a flaccid penis later. During hospitalization, the diagnosis of CML was confirmed by the peripheral blood smear exam and bone marrow aspiration. No impotency and other consequences were registered after his departure from the hospital.

The described cases proved the usefulness of participation of multidisciplinary teams consisting of clinicians of different specialties in management of patients with uncommon onsets of hematological malignancies. However, the management of CML with the life-threatening conditions, especially in the accelerated and acute phases, should be realized in the specialized inpatient wards with the support of Multi-Disciplinary Teams. Imatinib mesylate remains the first-line therapeutic option in chronic phase with low and intermediate Socal prognostic score, being superior to the conventional antineoplastic therapy and α-interferon due to the opportunity of achievement of a fast complete hematological remission, complete cytogenetic and molecular responses and due to the significant increase of the life quality and individual productivity, overall and relapse-free survival of CML patients [1] [3] [5] [6] [8] [9] [13]. Our study analyzed the uncommon onset of CML under the form of the ovarian apoplexy in a young female patient with Socal intermediate-risk score. Surgical treatment (suturation of the left ovary) was performed in order to manage this life-threatening health emergency prior to CML diagnosis. The targeted therapy with imatinib led shortly to a complete hematological remission, complete cytogenetic and major molecular response. The complete molecular response, thus, was achieved after a personalized targeted therapy with 2nd generation TKI nilotinib.

5. Conclusions

CML is a clonal myeloproliferative BCR-ABL-positive neoplasm, which some-

times may be complicated with the life-threatening emergencies, especially hemorrhagic and thrombotic events, infarct and rupture of the spleen, ovarian apoplexy, that require the involvement of the multidisciplinary team.

The ovarian apoplexy may serve as a presenting feature of CML in young females with a highly elevated leukocyte count. The reported CML case underwent successful personalized management with 2 consequent generations of TKIs, even if designated with Socal intermediate-risk score and complicated with ovarian apoplexy.

Author Contributions

Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing-original draft preparation, writing-review and editing, visualization, project administration.

Institutional Review Board Statement

The whole research protocol for CML studies was approved by the Research Ethic Board of the State University of Medicine and Pharmacy "N. Testemitanu".

Informed Consent Statement

The informed consent was obtained from the patient to assure the researcher and Research Ethic Board that the participant knows every aspect of participation in the study.

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Conflicts of Interest

The author declares no conflict of interest. The author does not have any financial relationships that might bias the content of this manuscript.

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