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Adult B-cell acute lymphocytic leukemia associated with osteolysis, but normal hematologic parameters – Rare case or related to treatment with mifepristone

Abstract

Though the presence of bone pain is common in children with Acute Lymphocytic Leukemia (ALL), it is uncommon in adults. A case is presented where CT-scan to evaluate back pain led to a biopsy and diagnosis of ALL. Though 95% of the marrow was replaced by lymphoblasts, perhaps this early diagnosis was the reason why all blood hematologic parameters were completely normal. Related to a delay of 6 weeks before chemotherapy could be given, the patient was treated with the progesterone receptor antagonist mifepristone to possibly prevent pancytopenia which could lead to death or serious morbidity before treatment could be rendered. The complete blood count six weeks later was still completely normal. Though mifepristone has been demonstrated to provide a significant extension of overall survival and considerable improved quality of life in a variety of advanced cancers, to date it had never been tried in humans with acute leukemia. However, there had been evidence that mifepristone could improve longevity and body conditioning scores in murine leukemia/lymphoma. Mifepristone has been found to suppress both messenger RNA and the Progesterone Induced Blocking Factor (PIBF) in a variety of leukemia cell lines. PIBF is the target for progesterone receptor antagonist therapy. Though only one case, this very well tolerated oral drug could be considered for treatment in ALL for elderly patients not candidates for intense chemotherapy, or those not responding to standard therapy, or in situations where there has been recurrence of acute leukemia.

Keywords: Adult B-cell lymphatic leukemia; Progesterone induced blocking factor; Bone pain; Membrane progesterone receptor; Progesterone receptor antagonist.

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Introduction

Acute Lymphoblastic Leukemia (ALL) is characterized by abnormal proliferation of clonal lymphoid progenitor cells in the bone marrow, periphery, or extramedullary sites. ALL is far more common in children than in adults [1]. In fact, ALL is the most common leukemia in children ages 1-4 [1].

Typical symptoms in children and adults alike are generally related to replacement of the bone marrow by these clonal lymphoid progenitor cells causing anemia, neutropenia, and thrombocytopenia leading to fatigue, infection and fever, and abnormal bleeding.

Children with ALL frequently complain of bone or muscle pain caused by proliferation of leukemia cells in the medullary canal causing a mass effect [2,3]. Normally bone pain is not associated with radiographic bone abnormalities. Osteolytic lesions may be found, however, in about 13% of children with ALL complaining of musculoskeletal pain [4]. This percentage may be falsely low because x-rays alone are not sensitive enough to detect spread to the bone in contrast to osteosarcomas or metastatic bone disease [5].

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There are several factors that could lead to osteolysis in ALL. In general, with ALL and other primary or secondary presence of cancer cells in the bone marrow, the interaction of cancer cells and the microenvironment of the bone marrow may lead to activation of osteoclasts and possibly suppression of osteoblasts. Another mechanism may involve the tumor secreting Parathyroid Hormone-Related Peptide (PTHrP) [6,7]. The cancer cells may also cause osteolysis by activating the receptor Activator of Nuclear-Kappa B Ligand (RANKL) or by the production of the osteoclast-stimulating factor by the bone niche including MIP-1a (a transforming growth factor-beta) and inflammatory cytokines, e.g., interleukin-6, tumor necrosis factor alfa, and interleukin-3 [8].

The symptoms related to bone pain may allow an earlier diagnosis of ALL before the classical previously mentioned symptoms occur from pancytopenia. Since ALL is much less common in adults vs. children, and musculoskeletal pain is much less common in adults vs. children, this combination has rarely been reported in adults. One case report of a 27-year-old female with acute ALL presented with paraparesis and multiple osteolytic lesions [9]. She did have moderate anemia (hemoglobin 8 g/dL) and mild decrease in total leukocyte count of 2,000 cmm and mild thrombocytopenia with a platelet count of 50,000/cmm. Her white blood count showed 12% lymphoblasts [9].

A second case of a 37-year-old male with osteolytic bone lesions had a normal white blood count and platelet count but had moderate anemia with a hemoglobin of 7.5 g/dL. In the 27-year-old female, bone marrow aspiration found 92% lymphoblasts and in the 37-year-old male bone marrow aspiration and biopsy demonstrated 80% of the cells were lymphoblasts [8,9]. We present another case of adult onset ALL diagnosed because of her musculoskeletal pain and osteolytic lesions, who presented with normal blood indices despite 95% of her marrow being replaced with lymphoblasts. Furthermore, we discuss the initial treatment with a progesterone receptor modulator that may have been responsible for keeping her complete blood count perfectly normal during the 6-week delay from diagnosis to treatment with intensive induction chemotherapy.

Case report

A 55-year-old woman, presenting with back pain, was diagnosed by bone biopsy to have Acute B cell Lymphoblastic Leukemia (ALL), even though her Complete Blood Count (CBC) was totally normal at that time. Even though she had no lymphadenopathy, and normal hematologic parameters, 95% of the bone marrow was replaced with lymphoblast cells. She made an appointment with a hematologist/oncologist at a major University Medical Hospital Medical Center. Unfortunately, the earliest she could be evaluated related to a busy schedule of the physicians was 6 weeks later. Through the help of a consultant from the Food and Drug Administration, her appointment was moved up by two weeks until she could be evaluated. She was subsequently treated with standard anti-leukemia drugs which was started 2 weeks after her initial consultation. Because of a 6-week delay in treatment, she was given 200 mg of oral mifepristone daily to try to prevent rapid progression of the acute leukemia leading to pancytopenia. The oncologist chose chemotherapy induction protocol of hyper fractionated Cyclophosphamide, Doxorubicin, Vincristine, and Dexamethasone (hyper CVAD).

Prior to starting the ALL-chemotherapy regimen, she had a CBC performed, and it was completely normal. Because of the requirement to have a PET scan done prior to initiation of the hyper CVAD, and because her insurance required outpatient PET scan, as mentioned, there was a delay in treatment for 6 weeks from the initial diagnosis by bone marrow biopsy. A repeat CBC immediately prior to hyper CVAD induction regiment was still completely normal.

The mifepristone was stopped when the hyper CVAD was started. After 9 months and surviving significant pancytopenia with replacement of hematologic factors, injection of granulocyte colony stimulating factor, and judicial use of antibiotics, a remission was achieved. She is now on mostly maintenance chemotherapy, and she has finally gained the strength to return to work. She still suffers from bone and muscle pain, but it is less severe after 1 year of chemotherapy and may be a side effect of her therapy rather than from bone lesions.

Discussion

After searching the literature, we could not find one case of adult-onset acute ALL that was diagnosed with a completely normal CBC. Since bone pain is common in children (occurring in over 40% of the cases), probably a perfectly normal CBC is possible because of early diagnosis. However, few cases of acute ALL with bone lesions and normal white blood count have been published even in children [4,5,10-12]. The early detection of this patient was related to the bone biopsy performed related to the diagnosis of bone lesions by MRI. With normal renal function, and normal serum calcium levels, and her age, the diagnostic suspicion was either multiple myeloma or solid cancer somewhere in the body with metastases to the bone.

With the bone marrow biopsy showing 95% lymphoblasts, a perfectly normal CBC was even more surprising. Possibly, at this stage, there was only patchy bone marrow involvement with still some normal areas that were not biopsied and were sufficient to provide, for a temporary time period, normal production of red blood cells, white blood cells, and platelets.

In the United States for adult patients diagnosed during 2005-2009, the 5-year survival was 44% for ALL which is certainly better than the dismal 18.2% for acute myeloid leukemia [13]. A priori, the best prognosis, in general, for all cancers is to treat it an early as possible before it has spread extensively. Unfortunately, treating ALL requires as experienced oncologic team knowledgeable of the best treatment options, and well equipped to handle the complications of intensive induction chemotherapy, especially pancytopenia, with potential for infection and bleeding disorders. Unfortunately, the earliest appointment that this major University oncology center could give her was in 4 weeks.

Progesterone Receptor (PR) modulators have been successfully used to provide a significant extension of life, and marked improvement of quality of life, in patients with a variety of advanced cancers with no more treatment options [14]. Though benefits have been found using various PR antagonists in cancers that are either positive for the classical nuclear PR or negative, the PR receptor antagonist used for treating most of the tumors devoid of the classical nuclear (n)PR has been mifepristone [14,15]. The use of PR antagonists was aimed at an immunomodulatory protein called the Progesterone Induced Blocking Factor (PIBF) that may be instrumental in helping both the fetal-placental unit and malignant tumor to escape immune surveillance [16-18]. Evidence supports the concept that the PR antagonist targets a membrane PR (mPR) responsible for PIBF production [19]. Though a PR antagonist also targets the nPR,

since the presence of the nPR is associated with less tumor virulence, the evidence suggests that the nPR helps to inhibit cancer proliferation, Thus, PR antagonists seen to work better for cancers devoid of the classical nPR [20].

Unfortunately, PR antagonists have not been tried in acute leukemia, though it seemed to prevent progression of Chronic Lymphocytic Leukemia (CLL) in an elderly woman who was treated with mifepristone, not for the CLL, but for rapidly advancing, probable, small cell lung cancer with the syndrome of inapprop0riate anti-diuretic hormone where it provided a marked beneficial effect [21,22].

Mifepristone has been found to suppress PIBF production by several human leukemia cell lines though an ALL-cell line was not tested [23]. In AkR/J mice bred to have a high frequency of spontaneous leukemia, who were very advanced at the time of treatment, in 61 mice gavaged with mifepristone (dosage based on 200 mg per day in humans) vs. 33 mice gavaged with olive oil, 50% of the controls were dead in 2 weeks vs. only 11.4% of those treated with mifepristone [24]. Furthermore, quality of life as evidenced by Body Conditioning Scores (BCS) showed a BCS of 5 (highest quality of life) that was present in 82% of mifepristone treated mice vs. 11% of controls [24].

Conclusion

The 55-year-old woman reported here had no side effects from mifepristone after 6 weeks of therapy. Given that 95% of her bone marrow showed lymphoblasts, it is likely that the treatment with mifepristone was responsible for the normal CBC 6 weeks after initial diagnosis of B cell ALL (though one cannot say for sure). Nevertheless, it could be that some other natural factor, other than treatment with a PR antagonist, inhibited progression to replace normal hematologic cells in the blood.

The 55-year-old patient was physically fit and in good health prior to back pain from the acute B cell ALL. Nevertheless, she has stated that if she has a recurrence of her ALL, or if it converts to Acute Myeloid Leukemia (AML), she will refuse any chemotherapy based on her past experience, and she stated that she definitely would refuse allogeneic Hematopoietic Stem-Cell Transplantation (HSCT). Instead, she stated that she would rather go back on mifepristone, or some other PR antagonist, even though there is no experience with long-term success with this treatment for ALL.

The prognosis is poor with recurrence of ALL or conversion to AML for adults in the United States. Whereas the 5-year survival was 44.0% for ALL it was only 18.6% for AML from 2005-2009 [13], and the treatment for recurrence after remission is even more extreme than initial induction therapy. Thus considering a poor quality of life during extensive treatment, with the knowledge that PR antagonists may extend a high quality of life to patients with a large variety of different cancers, even when all other treatment options have been explored, it may seem reasonable to offer this very well tolerated single agent mifepristone, PR antagonist as a therapeutic option [17]. This treatment option is supported not only by down-regulation in leukemia cell lines of the production of mRNA for PIBF and the PIBF protein by addition of mifepristone, but also inhibition of spontaneous leukemia in mice and the possibility that mifepristone was responsible for maintaining a normal CBC for 6 weeks despite 95% replacement of the bone marrow before mifepristone treatment in the patient described in this report.

For some elderly patients, who were not physically fit as our patient, for the same reasons, one could consider initial therapy with a PR antagonist. This would also apply to patients without insurance, or even with insurance who could not afford the expensive copays for the extremely expensive drug regimen and required hospitalization for acute leukemia. Many adult patients with ALL have no option other than hospice. Though mifepristone's use as an anticancer drug is considered an off-label use, a physician can obtain the drug from the manufacturer at a cost of $42 per pill in the United States. It is available in some countries, e.g., India and China, for less than one dollar per pill. In the United States, the physician must first gain approval from the manufacturer to receive the medication. If one can get a compassionate use investigative new drug approval from the United States Food and Drug Administration, the cost per pill is reduced by 50% with the drug released to the patient by the Feminist Majority Foundation. The experimental use of mifepristone for this patient was approved by a Western IRB.

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