ACUTE MYELOID LEUKAEMIA IN A 19 YEAR OLD PATIENT PREVIOUSLY TREATED FOR OSTEOSARCOMA - CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract. As patients with osteosarcoma become long-term survivors, increasing attention revolved around the burden of late effects. Recent studies showed an increase in the incidence of secondary malignant neoplasms in patients with osteosarcoma compared with the general population. The risk of developing leukaemia was reported to be in an increasing rate in the last decade. [1] Case report. In this report we present the case of a 19 year old patient diagnosed in the Haematology Department of Colentina Clinical Hospital in February 2015 with Acute Myeloid Leukaemia following the treatment (chemo- and radio-therapy) for an osteogenic osteosarcoma performed 3 years earlier. The cytogenetic examination revealed an abnormal karyotype with 91 chromosomes (XXY). The molecular biology exam did not find mutations in the FLT3ITD, FLT3D835 and NPM1 A genes. After the first induction course of chemotherapy the patient achieved complete remission, which was consolidated by 3 more courses of chemotherapy and an allogeneic stem cell transplant. Conclusion. Taking into consideration the prior treatment for osteosarcoma consisting in radiotherapy and chemotherapy we identified a secondary Acute Myeloid Leukaemia, this representing a major negative prognostic factor, along with the cytogenetic abnormalities found. These factors strongly indicate that the first complete remission should be consolidated by allogeneic stem cell transplant. Particularities of this case are the association of the two malignancies in a young patient, the presence of an abnormal karyotype (hyperploid), and also a good response to the induction therapy, thus achieving complete remission after the first induction course, and of course, sustaining that response.

Key words: secondary leukemia, osteosarcoma, cytogenetics, complete remission.

Introduction

It has been observed that the survival rate for patients with osteosarcoma (OS) has improved substantially with the introduction of multi-agent chemotherapy. As the number of paediatric cancer survivors increases, there is a concern about the development of secondary malignant neoplasms (SMN). [1] Osteosarcoma (OS) is the most common malignant bone tumour that affects adolescents and young adults. It is treated by surgery and pre- and postoperative chemotherapy. Various SMNs have been reported in OS patients. [2] Secondary Acute Myeloid Leukaemia (sAML) has also been reported in literature as a rare complication of OS. [3] However, the exact offending drug is difficult to prove as there is no consistent data. From the cited literature, sAML usually develops 2 years after completion of therapy. [4]

Different molecular and pathogenic agents may be involved in the development of second malignant neoplasms in long-term survivors of osteosarcomas. Some authors believe that the treatment with topoisomerase II inhibitors may have a role in the development of sAML, while others talk about cisplatin-associated sAML.

Case report

In this report we present the case of a 19 year old patient admitted in the Haematology Department of Colentina Clinical Hospital in February 2015 for fever (38°C), extreme fatigue, intense pallor. The patient had been diagnosed with osteogenic osteosarcoma of the right femur 3 years before which was operated and treated with chemotherapy (COSS EURAMOS protocol – Cisplatin, Doxorubicin, Methotrexate) and radiotherapy, achieving complete remission.

The symptoms which led him to our Department started approximately one month prior to the presentation at the hospital, and worsened over time.
At admission: physical examination revealed extreme pallor, no palpable lymph nodes, no organomegaly, fever (38°C); CBC: showed anemia (Hg=10.4g/dL, MCV=95fL, MCH=32pg), leukocytosis (WBC=116000/mmc) with lymphocytosis (Ly=100000/mmc) and thrombocytopenia (PLT=44000/mmc); Blood smear revealed myeloblasts in proportion of 97%; the DAT test was negative; LDH was high - 1055U/L (upper normal level=400U/L), normal uric acid value - 5.4mg/dL, normal renal and liver function (creatinine=0.74mg/dL, TGP=11.5U/L); inflammatory syndrome was present (ESR=95mm/h, CRP=42mg/dL); Negative serology for HIV, HBV, HCV; Bone marrow aspirate showed a percentage of 95% blasts with morphological characteristics of myeloid lineage, with the dislocation of normal hematopoiesis; Citochemistry performed showed 31% PAS positive cells and 3% myeloperoxidase positive cells; The flow-citometry performed on the bone marrow aspirate revealed 90% myeloblasts without maturation with the following phenotype: CD34+ CD33+ CD117+low cCD79a- cMPO+ cCD3- CD19- CD10- CD19- CD64+/; Cytogenetic exam revealed an abnormal karyotype with 91 chromosomes (XXY); The molecular biology did not find mutations in the FLT3 ITD, FLT3 D835 and NPM1 genes; 55% left ventricular ejection fraction; HLA phenotyping of the patient and his brother did not find them to be compatible.

In June 2015 the patient underwent an allogeneic stem cell transplant with a non-sibling donor, and the search for a compatible donor begun.

Meanwhile, he performed another 2 consolidation courses of chemotherapy; in this time a compatible donor was found and the allogeneic stem cell transplant was planned.

The bone marrow examination performed prior to the stem cell transplant showed a percentage of 2% blasts, emphasizing once again sustained complete remission.

The bone marrow examination performed prior to the stem cell transplant showed a percentage of 4% blasts. By this time, he was proposed for an allogeneic stem cell transplant with a non-sibling donor, and the search for a compatible donor begun.

Discussion

It is not uncommon for osteosarcoma patients to develop SMNs. The incidence is higher than the expected rate for benign bone tumors,[5] it is less than the reported incidence for Hodgkin's disease (9.7%) and retinoblastoma patients (30%).[6] The majority of SMNs in OS reported in literature are solid tumours of various organs or tissues.[7] It has been shown that the presence of p53 mutations in OS patients increases the incidence of non-therapy-related synchronous or metachronous SMNs.[8] Our patient had no family history of malignancy. The occurrence of sAML in OS is a rare complication. Very few cases have been reported either as part of large series of SMNs in OS[6] or as individual case reports.[5] The median time to develop SMNs after OS varies from 5.5 years to 7.6 years.[6] SAML developing after alkylating agents usually determines myelodysplasia, long latency period and monosomy 5 or 7 with AML (FAB type M1 or M2). Our patient was diagnosed with AML at 2 years from the end of the treatment for OS. sAML after topoisomerase II inhibitors have shorter latent time, FAB M4-M5 type and have translocation involving the MLL gene at chromosome band 11q23. The common topoisomerase II inhibitors are epipodophyllotoxins (etoposide, tenoposide) and anthracyclines (adriamycin, mitoxantrone). In this case the patient received treatment for OS with anthracycline based chemotherapy. No abnormality regarding the MLL gene was discovered. The reported minimum time to develop sAML was generally more than 1 year. However, Escudero et al.[9] reported that one of their case developed sAML after 7 months while our case developed sAML after 2 years. A majority of the reported cases of sAML after topoisomerase II inhibitors are due to etoposide.[10] The incidence of sAML in patients who received anthracyclines for the treatment of their primary tumours is not well known. In the series from Bacci et al.[5] of the 35 patients who received only anthracyclines, none developed sAML. The common drugs used for chemotherapy in OS are adriamycin, cisplatin and high-dose methotrexate, but ifosfamide, vincristine, bleomycin and carboplatin are also used. These chemotherapeutic drugs are not attributed to sAML commonly. Cisplatin has been reported for sAML

![Fig.1. Cytogenetics revealing abnormal cariotype – 91, XXY](image-url)

Considering all the investigations performed on admission, the patient was diagnosed with Acute Myeloid Leukaemia M1 FAB subtype (WHO 2008) and he started the first course of induction therapy with Cytarabine 5 days and Anthracycline 2 days – interrupted due to severe aplasia (the calculated total dose of anthracycline used for treating the osteosarcoma – 360mg – permitted us to further administer anthracycline this time as well).

The bone marrow aspirate performed on day 21st revealed a percentage of blasts of 4%, this being interpreted as complete remission.

Next, the patient underwent a first consolidation course of chemotherapy with high dose Cytarabine followed by a severe postchemotherapy aplasia. The bone marrow aspirate performed after this course revealed a percentage of 4% blasts, proving that the patient was in sustained complete remission.

By this time, he was proposed for an allogeneic stem cell transplant with a non-sibling donor, and the search for a compatible donor begun.

Meanwhile, he performed another 2 consolidation courses of chemotherapy; in this time a compatible donor was found and the allogeneic stem cell transplant was planned.

The bone marrow examination performed prior to the stem cell transplant showed a percentage of 2% blasts, emphasizing once again sustained complete remission.

In June 2015 the patient underwent an allogeneic stem cell transplant, which was well tolerated, and no major complications occurred following the stem cell transplant. Currently, we are waiting for the 90 day chimerism evaluation of the bone marrow in order to assess the procedure's success.
after germ cell tumours in young patients,[11] but not after OS treatment. It has been postulated that sAML in OS patients could be a synergistic effect of anthracyclins and cisplatin, which could be the likely cause in our case. [11] Our patient received chemotherapy containing both anthracycline and cisplatin.

Pyatt et al.[7] found no consistent relation between age at which chemotherapy was administered and development of sAML, and concluded that younger age was not a risk factor for the development of sAML. The time interval between completion of chemotherapy for the primary tumor and development of sAML depends on the type of chemotherapy used. Escudero et al.[3] reported a case of sAML after treatment for OS, who developed myelodysplastic syndrome 9 months after completion of chemotherapy for OS and evolved into sAML after 14 months. He also had deletion of long arm of chromosome 7. Because that patient had a short latency period and had only one dose of ifosfamide, the authors could not confirm the offending drug as alkylating agent.

Kawai et al.[12] while presenting two cases of sAML after OS treatment, compiled a series of 16 cases of acute leukaemia following treatment for primary OS. In that series, there were only 10 confirmed cases of sAML. Three had prior myelodysplastic syndrome, of which two developed sAML. The most consistent cytogenetic abnormality was t(8q;21q), which was seen in five patients. Our patient had a complex karyotype, 91, XXX. The prognosis of the patients with sAML is generally considered poor compared to de novo AML. [13] Review of SEER data showed 5-year survival in sAML as 23.7%.[14] However, some authors have refuted this and reported that survival could be equal to de novo AML, depending on the karyotyping abnormality.[15] Despite the poor prognostic factor given by abnormal cytogenetics our patient achieved complete remission after the first induction phase, sustained remission throughout the treatment and is currently in complete remission after the allogeneic stem cell transplant.

Conclusions

Considering the prior treatment for osteosarcoma consisting in radiotherapy and chemotherapy we identified a secondary Acute Myeloid Leukaemia, this representing a major negative prognostic factor, along with the cytogenetic abnormalities found (hyperploidy). These factors strongly indicate that the first complete remission should be consolidated by an allogeneic stem cell transplant.

The particularities of this case are the association of two malignancies in a young patient, the presence of an abnormal karyotype (hyperploidy), and also a good response to the induction therapy, this leading to complete remission after the first induction course, and of course, sustaining that response.

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