Acute Monoblastic Leukemia as a Second Malignancy After Doxorubicin and Cisplatin Treatment for Osteosarcoma

Sinan Mahir KAYIRAN, Namık ÖZBEK

Department of Pediatrics, Başkent University Faculty of Medicine, Ankara, TURKEY

ABSTRACT

Secondary or therapy-related acute myeloid leukemia (t-AML) occurs as a complication of various chemotherapy regimens. In pediatric age group, leukemia as a second malignancy after osteosarcoma treatment with doxorubicin and cisplatin is relatively rare. A 15-year-old girl was admitted to our hospital with signs and symptoms of leukemia. She had been treated one-year earlier with doxorubicin and cisplatin for osteosarcoma of the left femur. The patient was diagnosed with acute monoblastic leukemia on the basis of bone marrow examination and immunophenotype analysis. There were no cytogenetic abnormalities. The patient's father had been diagnosed with pelvic chondrosarcoma, which suggested a familial susceptibility to cancer. We interpreted this as a rare case of t-AML with normal cytogenetic analysis, and believe the disease was induced by the addition of platinum compounds to a regimen including topoisomerase II inhibitors.

Key Words: Therapy-related leukemia, Cisplatin, Doxorubicin, Osteosarcoma.

ÖZET

Doksorubisin ve Sisplatinle Osteosarkom Tedavisi Ardından İkincil Malignite Olarak Gelişen Akut Monoblastik Lösemi

Sekonder ya da tedaviye bağlı AML (t-AML) çeşitli kemoterapi rejimlerinin komplikasyonu olarak ortaya çıkar. Pediatrik yaş grubunda osteosarkom tedavisine sekonder malignite nadirdir. Onbeş yaşında bir kız çocuğu hastanemize akut lösemi yakınma ve bulguları ile başvurdu. Bir yıl öncesi sol femur osteosarkom tanısı ile doksorubisin ve sisplatin alan hastaya kemik iliği incelemesi ve immünfenotiplendirme ile akut monoblastik lösemi tanısı kondu. Sitogenetik anomali saptanmadı. Hastanın babası pelvik kondrosarkoma tanısı almış olup, ailesel yatkınlık düşünüldü. Biz bu olguyu sitogenetik anomalisi olmayan nadir bir t-AML olgusu olarak değerlendirdik ve nedeninin topoizomeraz II inhibitörleri içeren bir rejime platinum bileşikleri eklenmesi olduğuna inanmaktayız.

Anahtar Kelimeler: Tedaviye bağlı lösemi, Sisplatin, Doksorubisin, Osteosarkom.

Turk J Haematol 2003;20(1): 39-42

Received: *26.12.2001* ***Accepted:*** *20.04.2002*

INTRODUCTION

Leukemia occuring as a second malignancy after treatment of childhood malignancy is well recognized[1]. In most instances, the disease is of myeloid lineage and develops after chemotherapy and radiation therapy. The secondary leukemia known as therapy-related acute myeloid leukemia (t-AML) occurs as a complication of various chemotherapy regimens. This most often arises after leukemia and lymphoproliferative diseases and accounts for 10-20% of all AML cases[2]. The doxorubicin-cisplatin combination is a chemotherapeutic regimen that is commonly used in cases of osteosarcoma. Development of secondary leukemias after treatment of ovarian cancer with these two agents has been extensively reported and rewieved[3,4]. However, in pediatric age group, leukemia as a second malignancy in patients with primary osteosarcoma is relatively rare, and only isolated cases have been reported[5,6]. We report a case of secondary acute monoblastic leukemia that followed doxorubicin and cisplatin treatment for osteosarcoma.

A CASE REPORT

A 15-year-old girl was referred to pediatric hematology unit of our hospital with fever, abdominal pain, pallor, and gingival hypertrophy. Fourteen months earlier, she had had her left femur amputated due to osteosarcoma. She had received one presurgical cycle of chemotherapy with doxorubicin and cisplatin (100 mg/m^2 and 30 mg/m^2, respectively) and three cycles with the same agents and doses after amputation. The patient had remained well and in remission for one-year after the completion of chemotherapy, but then developed complaints of malaise, abdominal pain, and gingival hyperthrophy. She was admitted to hospital with these signs of acute leukemia. The family history revealed that the girl's father had undergone surgery for pelvic chondrosarcoma four-years earlier. Physical examination of the patient revealed aphthous stomatitis, gingival hypertrophy, abdominal tenderness and splenomegaly. The peripheral blood findings were as follows: Hemoglobin: 7.1 g/dL; white blood cell count: 232 x 10^9/L, with 98% of monoblasts in the differential count; platelet count 6 x 10^9/L. A bone marrow examination revealed hypercellularity with > 95% monoblasts. Immunophenotype analysis revealed: CD 13, 38.4%; CD 11B, 82.7%; CD 33, 98.6%; CD 45, 96.3%; CD 14, 50.7%. Based on these findings, she was diagnosed with acute monoblastic leukemia (AML-M5). Cytogenetic analysis revealed a 46 XX genotype with no chrosomal abnormalities. Other laboratory testing revealed elevated levels of blood urea nitrogen (56 mg/dL); creatinine (2.57 mg/dL), uric acid (25.1 mg/dL). The initial treatment was forced alkali diuresis and oral allopurinol. When the patient's uric acid values normalized and the WBC count dropped below 40 x 10^9/L, she was started on a remission induction protocol with prednisolone, cytosine arabinoside (ara-C) and daunorubicin. However, after 3 days of treatment the patient developed severe neutropenia and sepsis. She died 10 days later.

DISCUSSION

Many reports have identified acute leukemia as the most frequent therapy-related malignancy. The incidence of t-AML has increased in recent years due to long survival and intensive chemotherapy and irradiation protocols. Secondary leukemias have generally been divided into two groups: Those following treatment with alkylating agents, and those following topoisomerase inhibitor therapy. Alkylating agents are the main agents associated with the increased incidence of secondary leukemia. Cases that develop after exposure to these agents typically have a long latency period (5 or more years), are often preceded by a myelodysplastic syndrome (MDS) phase, and frequently show deletions or loss of chromosomes 5 and 7 on cytogenetic analysis[7]. In contrast, leukemias that follow exposure to topoisomerase II inhibitors usually have a short latency period (6-months-5-years), are not associated

with a prior MDS phase, and have monocytic or myelomonocytic morphology[8,9]. In our patient, the treatment-leukemia interval was relatively short in accord with topoisomerase II inhibitor induced secondary leukemia. The chemotherapy protocol that had been used was a doxorubicin-cisplatin combination. The most important mechanism of doxorubicin cytotoxicity is inhibition of topoisomerase II which results in breakage of DNA strands[10]. Cisplatin is a heavy metal complex that induces tumor cell death by cross-linking DNA strands in a manner analogous to that induced by alkylating agents. Reactive aquated intermediates form directly within cells and those intermediates covalently bind to DNA leading to DNA cross-links[11]. It is assumed that the addition of alkylating agents and platinum compounds to regimens containing topoisomerase II inhibitors may produce cumulative DNA damage sufficient to induce secondary leukemia[12].

The occurence of a second malignant neoplasm in patients treated for osteosarcoma has become an area of increasing concerns[13-18]. Bacci et al reported five patients who had a second neoplasm that was diagnosed 1 to 12 years (median, 6.1 years) from the beginning of treatment[19]. Two of these tumors were a lymphoblastic acute leukemia that became manifest 12 and 16 moths from the start of treatment. They were treated for the leukemia and were alive and free of disease 8 and 10 years after the last treatment. The treatment-leukemia interval and the chemotherapy regimen and dosage were almost the same in our patient, but the leukemia was the monoblastic type. In 1988, Orazi et al reported a child who developed acute monoblastic leukemia 2 years after chemotherapy for osteogenic sarcoma[6]. In this case, cytogenetic study showed a hyperdiploid complex pattern in all metaphases with 48XY, dup 1 (q12), +3, +9. Demuynck et al reported a similar case of t-AML with t(8;16) (p11;p13) following anthracycline-based therapy for nonmetastatic osteosarcoma[20]. The literature also documents cases of t-AML with no cytogenetic abnormality[21,22]. Similarly, the cytogenetic analysis in our case revealed no abnormalities. However, the fact that the patient's father had pelvic chondrosarcoma suggested a familial cancer susceptibility, which points to the need for further genetic evaluation.

In conclusion, if patients treated for primary malignancies were followed up more closely, more patients with therapy-related leukemia would be detected. As this patient with normal cytogenetic analysis is one of the rare cases of AML in the literature suspected to be related to doxorubicin and cisplatin treatment for osteogenic sarcoma, clinicians must be wary of leukemogenic potential of these agents. This case and careful follow-up of others that follow similar courses might help the confirm the hypothesis of cisplatin-related or doxorubicin-related secondary leukemias.

REFERENCES

1. Kapelushnik J, Dube I, Wilson P, Greenberg M. Acute lymphoblastic leukemia with t(4;11) translocation after osteogenic sarcoma. Cancer 1991;67:2887-9.
2. Smith MA, McCaffrey RP, Karp JE. The secondary leukemias: Challenges and research directions. J Natl Cancer Inst 1996;88:407-18.
3. Yokoyama Y, Futagami M, Fukushi Y, Sakamoto T, Higuchi T, Fujii S, Sato S, Takami H, Saito Y. Secondary acute nonlymphocytic leukemia following successful chemotherapy combining cisplatin, doxorubicin, and cyclophosphamide for stage IV epithelial ovarian cancer. Arch Gynecol Obstet 2000;263: 206-7.
4. Chambers SK, Chopyk RL, Chambers JT, Schwartz PE, Duffy TP. Development of leukemia after doxorubicin and cisplatin treatment for ovarian cancer. Cancer 1989;64:2459-61.
5. Meadows AT, Baum E, Fossati-Bellani F, Green D, Jenkin RD, Marsden B, Nesbit M, Newton W, Oberlin O, Sallan SG. Second malignant neoplasms in children: An update from the late effects study group. J Clin Oncol 1985;3:532-8.
6. Orazi A, Sozzi G, Delia D, Morandi F, Rottoli L, Cattoretti G. Acute monoblastic leukemia as a second malignancy following chemotherapy for osteogenic sarcoma. Pediatr Hematol Oncol 1988;5:39-46.
7. Pedersen-Bjergaard J, Pedersen M, Roulston D, Philip P. Different genetic pathways in leukemogenesis for patients presenting with therapy-related myelodysplasia and therapy-related acute myeloid leukemia. Blood

1995;86:3542-52.

8. Thirman MJ, Gill HJ, Burnett RC, Mbangkollo D, McCabe NR, Kobayashi H, Ziemin-van der Poel S, Kaneko Y, Morgan R, Sandberg AA. Rearrangement of the MLL gene in acute lymphoblastic and acute myeloid leukemias with 11q23 chromosomal translocations. N Engl J Med 1993;329:909-14.
9. Michael JT, Richard AL. Therapy-related myeloid leukemia. Hematol Oncol Clin North Am 1996;10: 293-320.
10. Zunino F, Capranico G. DNA topoisomerase II as the primary target of anti-tumor anthracyclines. Anticancer Drug Des 1990;5:307-17.
11. Dabholkar M, Reed E. Cisplatin. Cancer Chemother Biol Response Modif 1996;16:88-110.
12. Pui CH, Relling MV. Topoisomerase II inhibitor-related acute myeloid leukemia. Br J Haematol 2000; 109:13-23.
13. Winkler K, Beron G, Delling G, Heise U, Kabisch H, Purfurst C, Berger J, Ritter J, Jurgens H, Gerein V. Neoadjuvant chemotherapy of osteosarcoma: Results of a randomized cooperative trial (COSS-82) with salvage chemotherapy base on histological tumor response. J Clin Oncol 1988;6:329-37.
14. Provisor AJ, Ettinger LJ, Nachman JB, Krailo MD, Makley JT, Yunis EJ, Huvos AG, Betcher DL, Baum ES, Kisker CT, Miser JS. Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: A report from the Children's Cancer Group. J Clin Oncol 1997;15:76-84.
15. Fuchs N, Bielack SS, Epler D, Bieling P, Delling G, Korholz D, Graf N, Heise U, Jurgens H, Kotz R, Salzer-Kuntschik M, Weinel P, Werner M, Winkler K. Long-term results of the co-operative German-Austrian-Swiss osteosarcoma study group's protocol COSS-86 of intensive multidrug chemotherapy and surgery for osteosarcoma of the limbs. Ann Oncol 1988;9:893-9.
16. Pappo A, Schneider NR, Sanders JM, Buchanan GR. Secondary myelodysplastic syndrome complicating therapy to osteogenic sarcoma. Cancer 1991; 68:1373-5.
17. Beattie EJ, Harvey JC, Marcove R, Martini N. Results of multiple pulmonary resections for metastatic osteogenic sarcoma after two decades. J Surg Oncol 1991;46:154-5.
18. Pratt CB, Meyer WH, Luo X, Cain AM, Kaste SC, Pappo AS, Rao BN, Fleming ID, Jenkins JJ 3rd. Second malignant neoplasms occuring in survivors of osteosarcoma. Cancer 1997;80:960-5.
19. Bacci G, Ferrari S, Bertoni F, Ruggieri P, Picci P, Longhi A, Casadei R, Fabbri N, Forni C, Versari M, Campanacci M. Long term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the instituto ortopedico rizzoli according to the instituto ortopedico rizzoli/osteosarcoma-2 protocol: An updated report. J Clin Oncol 2000;18: 4016-27.
20. Demuynck H, Verhoef GE, Zachee P, Vandenberghe P, Van Orshoven A, Paridaens R, Samson I, Boogaerts MA. Therapy-related acute myeloid leukemia with t(8;16)(p11;p13) following anthracycline-based therapy for nonmetastatic osteosarcoma. Cancer Genet Cytogenet 1995;82:103-5.
21. Ellis M, Ravid M, Lishner M. A comparative analysis of alkylating agent and epipodophyllotoxin–related leukemias. Leukemia and Lymphoma 1993;11:9-13.
22. Özbek N, Çetin M, Tuncer AM, Yetgin S. Secondary acute myeloblastic leukemia in a child with acute lymphoblastic leukemia treated with epipodophyllotoxins. Turk J Pediatr 1995;37:279-82.

Address for Correspondence:

Sinan Mahir KAYIRAN, MD

Başkent University Faculty of Medicine
Department of Pediatrics
6. Cadde, No: 72/3,
06490, Bahçelievler, Ankara, TURKEY

e-mail: *sinanmahir@yahoo.com*