PEDIATRIC & ADOLESCENT OSTEOSARCOMA ...
PROGRESS FROM THE PAST, PROSPECTS FOR THE FUTURE

March 5 - 8, 2008

Symposium Syllabus

The University of Texas M. D. Anderson Cancer Center
Robert C. Hickey Auditorium, 11th Floor
R. Lee Clark Clinic
1515 Holcombe Boulevard
Houston, Texas

THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER®

children's cancer hospital™

Notes on Epidemiology and Etiology of Osteosarcoma

Giulia Ottaviani, MD, PhD

EPIDEMIOLOGY AND ETIOLOGY OF OSTEOSARCOMA: A COMPENDIUM OF NOTES ABSTRACTED FROM THE LITERATURE

Giulia Ottaviani, MD, PhD*°; Norman Jaffe, MD, ScD*

*Children's Cancer Hospital, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

°Anatomic Pathology, University of Milan, 20122 Milan, Italy

Osteosarcoma derives from primitive bone-forming mesenchymal cells and is the most common primary bone malignancy. According to the most recent report from the U.S. Cancer Statistics Working Group, the incidence rates and 95% confidence intervals of osteosarcoma for all races and both sexes are 4.0 (3.5-4.6) for the range 0-14 years and 5.0 (4.6-5.6) for the range 0-19 years per year per million persons. Among childhood cancers, osteosarcoma occurs eighth in general incidence and in the following order: leukemia (30%), brain and other nervous system cancers (22.3%), neuroblastoma (7.3%), Wilms tumor (5.6%), Non-Hodgkin lymphoma (4.5%), rhabdomyosarcoma (3.1%), retinoblastoma (2.8%), osteosarcoma (2.4%), Ewing sarcoma (1.4%). The incidence rates of childhood and adolescent osteosarcoma with 95% confidence intervals are: Blacks 6.8 / year /million, Hispanics 6.5 / year / million and Caucasians 4.6 / year /million.

Osteosarcoma has a bimodal age distribution, having the first peak during adolescence and the second peak in older adults. The first peak is in the 10 to 20-year-old age group, coinciding with the pubertal growth spurt. This suggests a close relationship between the adolescent growth spurt and osteosarcoma. Osteosarcoma patients whose disease is diagnosed during their growth spurt are generally taller than average, while patients identified in adulthood have average height. The second osteosarcoma peak is in adults older than 65 years of age in which osteosarcoma is more likely to represent a second malignancy, frequently related to Paget's disease. Approximately 1% of patients with Paget's disease develop osteosarcoma.

Osteosarcoma commonly occurs in the long bones of the extremities near the metaphyseal growth plates. The most common sites are femur (42%, with 75% of tumors in the distal femur), tibia (19%, with 80% of tumors in the proximal tibia), and humerus (10%, with 90% of tumors in the proximal humerus). Other locations of note are the skull or jaw (8%) and pelvis.

The overall 5-year survival rate for osteosarcoma is 68%., without significant gender difference. Age of the patient is correlated with survival with the poorest survival for older patients. Complete surgical excision is important to ensure an optimum outcome. Tumor staging, presence of metastases, local recurrence, chemotherapy regimen, anatomic location, size of the tumor, and percentage of tumor cells destroyed after neoadjuvant chemotherapy have variable effects on outcome.

The etiology of osteosarcoma is still largely unknown, but there may be a relationship to growth, since it coincides with a period of rapid bone growth in young people. Rapidly proliferating cells may be particularly susceptible to oncogenic agents and mitotic errors which lead to neoplastic transformation. Genetic aberrations that accompany osteosarcoma have received increasing recognition as an important factor in its etiology. Osteosarcoma tumor cells exhibit karyotypes with a high degree of complexity which has made it difficult to determine whether any recurrent chromosomal aberrations characterize osteosarcoma. Although extremely rare, osteosarcoma has occasionally been observed in several members of the same family. No other clinical abnormalities in the proband or the affected members were reported.Pathologic examination of the tumors revealed no unusual features. Genetic testing in most of these reports was not available. The patients generally responded to conventional therapy. A genetic predisposition to osteosarcoma is found in patients with hereditary retinoblastoma, characterized by mutation of the retinoblastoma gene RB1 on chromosome 13q14. The Rothmund-Thomson syndrome is an autosomal recessive disorder with a heterogeneous clinical profile. Patients may have a few or multiple clinical features including skin rash, small stature, skeletal dysplasias, sparse or absent scalp

hair, eyebrows or eyelashes, juvenile cataracts, and gastrointestinal disturbance including chronic emesis and diarrhea; its molecular basis is the mutation in the RECQL4 gene in a subset of cases. The Li-Fraumeni syndrome is an autosomal dominant disorder characterized by a high risk to develop osteosarcoma and has been found in up to 3% of children with osteosarcoma. It is associated with a germline mutation of the p53 a suppressor gene. The following three criteria must be met for a diagnosis of Li-Fraumeni syndrome: 1) A proband diagnosed with sarcoma when younger than 45 years; 2) A first-degree relative with any cancer diagnosed when younger than 45 years; 3) Another first- or second-degree relative of the same genetic lineage with any cancer diagnosed when younger than 45 years or sarcoma diagnosed at any age. A second recessive p53 oncogene on chromosome 17p13.1 may also play a role in the development and progression of osteosarcoma.

Osteosarcoma has also been associated with solitary or multiple osteochondroma, solitary enchondroma or enchondromatosis (Ollier's disease), multiple hereditary exostoses, fibrous dysplasia, chronic osteomyelitis, sites of bone infarcts, sites of metallic prostheses and sites of prior internal fixation. Ionizing radiation is a well-documented etiologic factor, being implicated in approximately 3% of osteosarcoma cases. Osteosarcoma has also been associated with the use of intravenous radium and Thorotrast. Exposure to alkylating agents may also contribute to its development and is apparently independent of the administration of radiotherapy.