



EDITORIAL

Bone Involvement in Neuroblastoma

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Neuroblastic tumors (ie, neuroblastoma, ganglioneuroblastoma, ganglioneuroma) are the most common extracranial solid tumors in children.¹ Neuroblastoma (NB) accounts for almost 8% of childhood malignancies. Its prognosis is extensively variable, ranging from spontaneous regression to fatal disease in spite of receiving multimodality therapy.¹ Screening programs of infants show that many cases escape detection because of spontaneous regression or maturation into benign lesions. Derivation from precursors of the sympathetic nervous system accounts for (a) primary sites in adrenal glands and in paraspinal locations from neck to pelvis and (b) high urinary levels of catecholamines in 90% of cases.²

This embryonal neoplasm frequently invades vascular structures and usually presents with substantial metastatic disease in bone, bone marrow, lymph nodes and liver; spread to brain is observed and lung metastasis has been reported very rarely to a maximum of 3.6%.³ Hence, defining disease extension and precise staging requires imaging studies such as computerized tomography scans (or MRI), bone scan, metaiodobenzylguanidine (MIBG) scan, bone marrow (BM) examinations and biopsy and urine catecholamine measurements.⁴

Multiple imaging and clinical tests are needed to accurately assess patient risk with risk groups based on disease stage, patient age, and biological tumor markers.¹⁻⁴

Around 60% of patients with NB have metastatic disease at diagnosis mostly involving bone marrow or cortical bones.^{1,2}

Since the spread of tumor cells to the BM is a dismal prognostic sign for patients with NB, obviously searching for BM infiltration is of the most prominence for both staging and therapeutic purposes.⁵

Due to the International Neuroblastoma Staging System, the presence of metastasis in BM is assessed by morphological study of BM smears and trephine biopsies.^{4,5} Bone involvement is detected in 55– 68% of patients who have metastatic disease at diagnosis.^{5,6} Bone lesions affected by metastatic tumor cells are conventionally divided into two categories ; osteolytic and osteoblastic.⁶

Main contributors in osteolytic lesions are osteoclast activating factors such as parathyroid hormone-related protein (PTHrP) which stimulates osteoclast maturation and in osteoblastic lesions there are factors that stimulate osteoblast proliferation, differentiation and bone formation.⁷ Regularly, both osteoclastic and osteoblastic processes are observed simultaneously. Hence, osteoclast inhibitors like bisphosphonate compounds have begun to be used and demonstrate encouraging results.^{7,8}

The mechanisms involved in the formation of bone metastasis in NB have now begun to be elucidated. It

is documented that, as observed in breast cancer and multiple myeloma, NB bone metastases are predominantly osteolytic.⁸ Sohara et al. exploiting a model of bone invasion in immunodeficient mice, revealed that NB cells recruited osteoclasts to produce osteolytic lesions and invade the bone matrix.⁹ So in support of a causative role for osteoclasts in NB bone invasion, they used treatment with the bisphosphonate compound; ibandronate, which showed a dramatic delay in the progression of osteolytic lesions.⁹ The existing data strongly suggest that bisphosphonates may be clinically effective in the treatment of bone metastases in neuroblastoma.⁹

Promising outcomes of trials in the animal models of bone metastasis and invasion in NB terminated to the allowance for the testing of novel therapeutic pathways more particularly focused towards bone metastasis in human neuroblastoma.¹⁰

A first target is osteoclasts since it has now been clearly clarified that bone metastasis in neuroblastoma is primarily an osteolytic process associated with an increased activation of osteoclasts. Over the last decade several inhibitors of osteoclast activation have been developed.^{9,10}

Proper staging and monitoring of patients with neuroblastoma is profoundly dependent on scintigraphic studies. Tc-99m-MDP scan has long been known to be superior to skeletal survey for detecting metastases in cortical bone.¹¹

Functional imaging with 123I-MIBG scintigraphy is a crucial tool in patients with NB both for initial staging and also response to therapy, allowing visualization of the primary tumor and metastatic lesions in the various sites including the bones.^{11,12}

Various radiopharmaceuticals for positron emission tomography (PET) such as fluorine-18-fluorodeoxyglucose (18 F-FDG), fluorine-18-dihydroxyphenylalanine (18 F-DOPA), 68Ga-labelled somatostatin analogues, 11C-hydroxyephedrine (11C-HED) and 124I-MIBG are currently under investigation.¹²

Treatment protocols for NB are stratified according to risk which is outlined on the basis of biologic and clinical prognostic factors. Treatment of high-risk NB continues to be a challenge, with a high rate of relapse in the bone and bone marrow.^{11,12}

More to add, high quality Tc99m-MDP bone scan images are required if the skeletal metastases of neuroblastoma, which commonly develop in the metaphyses of long bones, are to be detected.¹³ Meanwhile, it plays a crucial role in follow-ups of neuroblastoma in children who present with bone involvement initially.^{12,13}

Skeletal involvement in neuroblastoma can be focal or diffuse and sometimes bilaterally symmetrical. These abnormalities can be recognized on MDP bone scan only with expertise and meticulous attention to technical details.^{9,13}

These alterations which have been traced on MDP bone scan during follow-ups are beneficial in evaluating the effects of the initial treatment as well as further modification of the treatment plan.¹⁴ Peng et al. demonstrated that zoledronic acid has a dual

antiosteoclastic and antitumoral activity. The data emphasize that bisphosphonate in combination with cytotoxic chemotherapy in mice with established osteolytic lesions ended in preventing bone degradation and also extending survival, so could be trialed in children with neuroblastoma that has metastasized to the bone.⁸

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