Pre-Congress Symposium 2 (Bone & Joint / Oncology / GEMO)
Saturday, October 13, 09:00-12:00

Session Title
Nuclear Medicine Management of Bone Metastases in the Era of Targeted Treatments

Chairpersons
Tim Van Den Wyngaert (Edegem)
Mohsen Beheshti (Linz)

Programme

09:00 - 09:25 Philippe Clézardin (GEMO, Lyon): Bone Oncologist's View - Bone Metastases Therapies in the Era of Targeted Treatments

09:25 - 09:50 Jean-Marc Guinebretière (GEMO, Saint-Cloud): Pathologist's View - Bone Response and Molecular Targets for Imaging

09:50 - 10:15 Frédéric Paycha (Paris): Bone Targeted Tracers

10:15 - 10:45 Coffee Break

10:45 - 11:10 Mohsen Beheshti (Linz): Tumor Targeted Tracers

11:10 - 11:30 Torsten Kuwert (Erlangen): Quantification

11:30 - 12:00 Egesta Lopci (Milan): See the Forest for the Trees - RECIST, PERCIST, iRECIST, and PCWG-2?

Educational Objectives

1. To get acquainted with immunotherapy and targeted-therapy armamentarium
2. To acquire the basics of main cross-talks between tumoral metastases, bone and bone marrow environments
3. To synthetize principles, strengths, and limitations of international standardized systems in clinical use for therapy assessment of bone metastases (RECIST, MDA, PERCIST, iRECIST,..)

Summary

The establishment of bone metastasis activates several immunosuppressive mechanisms. Hence, understanding the tumor-bone microenvironment is crucial to inform the development of novel targeted therapies. The advent of newer immunotherapeutic and molecularly targeted agents has provided a number of effective options for cancer treatment but has also added much complexity in selecting the best initial treatment or treatment plan for each patient. Molecularly targeted agents offer selectivity and are the cornerstone for precision medicine.
While targeted agents are associated with high tumor response rates, patients inevitably develop resistance to these drugs. Immunotherapies exploit the endogenous immune system to eradicate cancer and can produce durable disease control that results in long-term, treatment-free survival in some patients.

Migration of cancerous cells to skeletal tissue occurs frequently in many types of cancer where bone is one of the most common metastatic target sites particularly for prostate and breast cancer. The clinical application of bone-targeted agents in current clinical practice is mostly focused on the inhibition of osteoclast activity.

Bisphosphonates, chelated radionuclides, strontium compounds, tetracycline, and some metals all are utilized for either therapy or diagnosis due to their hydroxy-apatite targeting ability. Other key bone-specific targets for drug intervention include the cells in bone and bone marrow or the signaling systems involved in their regulation.

Not only tumour cell membrane receptors and proteins, but also soluble tumour specific targets present in the tumour micro-environment can be visualised with molecular imaging. Vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGFβ) are such targets. VEGF is an important factor involved in tumour angiogenesis.

In cancers with a high incidence of bone metastases, there are 3 classes of immunotherapies that have been approved. The first, immune checkpoint inhibitors include anti-PD-1 antibodies, anti-CTLA-4 antibodies, anti-PD-1), and anti-PD-L1 antibodies. The next class is cytokine therapy which includes interferon alpha, and interleukin-2. Both of these cytokines induce T-cell proliferation. The dendritic cell therapy sipuleucel-T promotes stimulation of prostate cancer antigen specific T-cells. The bone-metastatic microenvironment displays a unique immune phenotype that could result in a distinct pattern of response to immune therapy when compared to other metastatic sites.

Bone-seeking radio-isotopes, such as 153Sm ethylene diamine tetramethylene phosphonate and 89Sr chloride, have been used successfully for palliation of pain from bone metastases. One of the major recent strides has been the development and approval of an alpha-particle bone-seeking radionuclide for treatment of bone metastases: radium-223 chloride (Ra-223). However, Ra-223, which is an alpha emitter, is not just a bone-targeted agent but a mixed therapeutic agent (efficient to lessen skeletal-related events, and to increase overall survival). Similarly, PSMA has recently emerged as an important target in prostate cancer, leading to production of 177Lu-conjugated small molecule ligands of PSMA.

The measurable lesions approach excludes many breast and prostate cancer patients from response evaluation according to RECIST as bone metastases are the most common (and frequently the only) site of distant metastases. Currently bisphosphonates-(99mTc) scintigraphy is the standard staging method to detect bone metastases. However, for response evaluation, bisphosphonates-(99mTc) scintigraphy is suboptimal, since it takes 6 months or longer to reliably detect a response.

In the respect of therapeutic assessment, quantification of skeletal tumoral burden may be approached through dedicated software packages.

Alteration of response criteria is mandatory in order to circumnavigate miscellaneous diagnostic imaging loop-holes induced by targeted therapies and immunotherapies (eg false negative bisphosphonates-(99mTc) scans induced by Tyrosine Kinase Inhibitors, false-positive bisphosphonates-(99mTc) scans induced by proteasome inhibitors). Such new sets of criterias have resulted in iRECIST endeavor; similar efforts must be developed for metabolic imaging.

PET imaging of PD-L1 expression and other targets (immuno-PET) will help further elucidate responders versus nonresponders to therapy, as imaging is potentially better suited to the spatiotemporal varying expression patterns of immune checkpoint molecules.