Insights to biology and immunotherapy of osteosarcoma

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Osteosarcoma is the most common primary tumor of the bone with the highest incidence in the first two decades of life. The incidence rate with 95% confidence is 4 for the range of 0-14 and 5 for the range of 0-19 cases per million per year. Osteosarcoma is a rare malignant mesenchymal tumor with presence of mesenchymal cells and production of osteoid matrix (1). Distinct histological subtypes have been defined, but the biological behavior and the conventional approach to treatment have been similar for last couple of decades without improvement in outcome. The biology of osteosarcoma is characterized with a high rate of lung metastasis. Disorganized genome seems to be the best description of genetic aberrations and changes in gene expression in osteosarcoma, with the most consistent finding, beside the p53 and RB dysregulation, significant aneuploidy and some evidence of massive disruption in the chromosomal structure (2). The metastatic cascade represents a process where cell leaves primary tumor and invades the surrounding tumor microenvironment with intravascular and also extravascular invasion to the distant sites enabling the blood supply and growth to the secondary site and reengage to the new microenvironment. Meanwhile, metastatic cell could be dormant in the „protective” environment and then move to the secondary distant sites (3). The microscopic metastases are usually responsible for disease progression, so targeting genetic and epigenetic alterations will certainly improve the outcome (2). Recent studies showed that metastatic clones often do not correspond to the dominant clones in the primary tumor, but may evolve monoclonal and polyclonal, showing the clonal/subclonal heterogeneity of osteosarcoma. At the same time, immune response is a complex process that combines recognition of tumor cells, and response of effector and regulatory immune cells. Tumor cells by soluble factors secretion lead to downmodulation of the immune system. The well known immune „escape” is the hallmark of cancer when immune system play a dual function, slowing down the tumor progression at first and then facilitating the tumor growth after the modelling phase of tumor cells. How to switch immunotolerance which contribute to permissive microenvironment beneficial for tumor cells to immunocompetent environment, is the challenge of immunotherapy (4). Two mains immunotherapeutic approaches are proposed for bone sarcomas. The first one is based on targeting the pro-tumoral effectors including M2 macrophages, i.e. muramyl tripeptide phosphatidylethanolamine (MTP-PE), interferon gamma (IFNγ) and the molecules associated with immune checkpoints; programmed death-ligand 1 (PD-L1) with it’s receptor, programmed cell death protein (PD1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). The other one is based on the stimulation of anti-tumoral effectors; dendritic cells (DC), nitrogen containing bisphosphonates (N-BPs) and natural killer cells (NK). MTP-PE is a drug registered by European Medicinal Agency (EMA) for postoperative treatment of high-grade osteosarcoma. Recently, we have started to apply MTP-PE in Croatia, and in time, we will see the results. The concept of chimeric antigen receptor (CAR) T-lymphocytes (CAR T-cells) has been developed to bypass the human leukocyte antigen restrictions, so diverse CAR T-cells have been developed based on this concept (CAR T-cells targeting B7-H3) (5). The SARC028 clinical trial revealed an interesting clinical response which highlight a major difference between adult and pediatric cancers that may be explained by low expression of neoantigens in addition to their specific microenvironment.

Attenuated oncolytic viruses inoculated directly into tumor mass or delivered by macrophages have been proposed as one of the options also. However, the low immunogenicity of pediatric tumors will require other approaches with full

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molecular profiling of all bone sarcomas. This is mandatory in order to establish targetable biomarkers for better identification and selection of patients for specific therapies.

**Abbreviations:**

- **MPP PE** – Muramyl tripeptide phosphatidylethanolamine
- **IFNγ** – Interferon gamma
- **PD-L1** – Programmed death-ligand 1
- **PD1** – Programmed cell death protein
- **CTLA-4** – Cytotoxic T-lymphocyte-associated antigen 4
- **DC** – Dendritic cells
- **N-BPs** – Nitrogen containing bisphosphonates
- **NK** – Natural killer cells
- **CAR** – Chimeric antigen receptor
- **CAR T-cells** – T-lymphocytes

**REFERENCES**