

Preventing relapse in pediatric metastatic osteosarcoma using evolutionary-informed approaches.

Background: Osteosarcoma (OS) is the most common cancer of bone and its peak incidence occurs during the growth spurt in adolescents and young adults. Despite concerted efforts, the cure rate has not changed since chemotherapy was first added to surgery in the early 1980's. All patients receive 10 weeks of chemotherapy, surgery to resect the primary tumor, and an additional 19 weeks of chemotherapy when disease is localized and only detectable at one site. The prognosis is worse when the primary tumor has <90% necrotic cells post-resection, or when there is evidence of metastasis – virtually always in the lung – with number of metastases correlating with outcome. All sites of disease require surgical removal for a reliable chance of remission. In localized patients and in patients with oligometastatic presentation where individual lesions are surgically removed, relapse occurs because of the outgrowth of lung metastases that were below the detectability thresholds. Whether this subclinical population's resistance is due to dormancy, molecular or mutational acquired changes, or stochasticity is unknown. Currently, after the completion of surgery and neoadjuvant plus adjuvant chemotherapies, no therapeutic interventions are performed until evidence of relapse.

Hypothesis: Therapeutic interference during remission can suppress or prevent relapse, leading to superior clinical outcomes compared to starting interventions after the detection of the relapse. Our preliminary modeling studies suggest that understanding the origin of relapsing metastases is critical for defining the approach to suppress the relapse. Recurrent metastases may arise either from 1) growing metastases with at least partial resistance to the therapy, or 2) dormant tumor cells that escape the impact of therapy and give rise to progressive metastatic disease that subsequently is responsive to therapy.

Aim 1. Define the origin of relapsing tumors. Understanding the origin of relapsed metastatic disease is key to define optimal approaches to disrupt the relapse.

1a. Define presence of micro-metastatic disease and individual dormant tumor cells in lung tissue of osteosarcoma patients. We will take advantage of the fact that surgical removal of metastatic tumors typically requires removal of lung wedges with normal tissue, which is left out from pathology analyses. Through IHC staining of OS specific markers, we will analyze the ostensibly healthy tissue for the presence of disseminated dormant tumor cells as well as metastatic lesions below the detectability threshold. The data will be extrapolated to the whole lung to estimate their absolute and relative numbers.

1b. Using growth rate estimates, derived from observed growth rates of metastatic lesions in the absence of therapy challenge, we will define the putative time of origin of the lesions. Tracing initiation of growth to the time of therapy would indicate the origin from actively growing undetected tumors. Conversely, tracing the initiation post therapy would indicate origin from a dormant tumor cell.

1c. Using modeling approaches developed during the workshop, we will update model assumptions based on patient derived data and define optimal treatment strategies.

Aim 2. Test strategies to suppress outgrowth of metastatic lesions. Transition from growth in a primary disease site toward growth in the lung microenvironment is associated with epigenetic reprogramming and, potentially, with new genetic variability. Suppressing epigenetic and genetic variegation could limit relapse, and can be achieved with relatively well-tolerated inflammation targeting strategies. Whereas the main benefit would be achieved against disseminated dormant tumor cells, there is early evidence that anti-inflammatory strategies might also suppress outgrowth of established microscopic metastases.

2a. Test for the ability of anti-inflammatory therapies to suppress formation of metastatic lesions in a panel of xenograft mouse models of OS, using an anti-inflammatory regimen combining IL1 and COX2 inhibitors.

2b. Given that modulation of inflammation could impact immune surveillance, which in turn could be important for the modulation of metastatic outgrowth, we will also interrogate the impact of anti-inflammatory strategies in immuno-competent syngeneic mouse models.

Successful implementation of these proposed studies will elucidate the origin of metastatic relapse, providing a critical mechanism to inform model-assisted therapy optimization efforts and thereby opening doors to advance therapeutic outcomes both for (neo) adjuvant treatment and maintenance therapies. Should we find that inflammation targeting therapies could suppress metastatic outgrowth, this strategy could be implemented clinically during the remission phase.