Clinical Trial

Major Finding: Brentuximab vedotin plus chemotherapy produced an overall survival rate of 98.7% after 3.4 years.

Concept: This antibody–drug conjugate reduced the need for radiotherapy relative to that in prior trials.

Impact: Brentuximab vedotin may enable prevention of some radiation-linked late-occurring adverse events.

BRENTUXIMAB VEDOTIN MAY CUT RADIATION USE IN PEDIATRIC HODGKIN LYMPHOMA

The prognosis for pediatric patients with classic Hodgkin lymphoma, even the high-risk subtype, is favorable; however, treatment requires chemotherapy and radiotherapy that may cause adverse events in the long term. In an open-label, single-arm clinical trial enrolling 77 pediatric patients with high-risk Hodgkin lymphoma, Metzger and colleagues evaluated the use of the CD30-targeting antibody–drug conjugate brentuximab vedotin in place of vincristine in standard OEPA or COPDac (vincristine plus etoposide, prednisone, and doxorubicin or cyclophosphamide plus vincristine, prednisone, and dacarbazine, respectively) therapy to determine whether brentuximab vedotin, which is approved for adults with the same malignancy, could reduce the use of radiotherapy. Following brentuximab vedotin and chemotherapy treatment, only lymph nodes that did not exhibit a complete response at the early response assessment were irradiated. After a median follow-up period of 3.4 years, the event-free survival rate was 97.4% (75 of 77 patients) and the overall survival rate was 98.7% (76 of 77 patients). The death occurred unexpectedly due to ventricular tachycardia during cycle 4 of chemotherapy, suggesting that monitoring for this condition is warranted, but the treatment regimen otherwise had an adverse event profile similar to that expected given the individual therapies administered. Notably, the nodal responses allowed for radiotherapy to be omitted in 35% (27 of 77 patients) of treated patients, and the exposure of normal tissue to radiation was substantially reduced relative to exposures in a prior trial by the same group that enrolled a similar patient population. In summary, the results of this study provide evidence that the substitution of brentuximab vedotin for vincristine in standard OEPA or COPDac is safe and effective and that this treatment regimen may enable reduced use of radiotherapy, potentially preventing late-occurring adverse events owing to radiation exposure. ■

Metzger ML, Link MP, Billett AL, Flerlage J, Lucas Jr JT, Mandrell BN, et al. Excellent outcome for pediatric patients with high-risk Hodgkin lymphoma treated with brentuximab vedotin and risk-adapted residual node radiation. J Clin Oncol 2021 Apr 7 [Epub ahead of print].

Metastasis

Major Finding: The bone microenvironment induced metastatic cancer cells to further disseminate to other organs.

Concept: The bone microenvironment enhanced secondary metastasis via EZH2-mediated epigenetic reprogramming.

Impact: This work shows that the bone-metastatic niche can play a key role in seeding secondary metastases.

BONE MICROENVIRONMENT PROMOTES FURTHER SPREAD FROM PRIMARY METASTASES

Metastasis of cancer cells from primary tumors to secondary sites accounts for the majority of cancer-related deaths, and recent work has suggested that existing metastases can seed secondary metastases. Because bone is not only the most common but also often the first site of breast cancer metastasis, Zhang, Bado, and colleagues developed a preclinical model to investigate mechanisms that may underpin metastatic dissemination from bone lesions. When human breast cancer cells were injected into mice via the intrailiac artery, tumors first formed in bone at early timepoints, followed by the establishment of metastatic lesions in distant organs after several weeks. When compared with injections via the intrailiac vein or orthotopic injections into the mammary fat pad, intrailiac artery injections resulted in more rapid and widespread secondary metastases, suggesting that the bone microenvironment to which cancer cells are exposed following intrailiac artery injection enhanced the metastatic phenotype. A parabiosis model involving the fusion of circulation between a bone lesion–carrying donor mouse and a tumor-free recipient showed that, although shared circulation was not enough for efficient metastatic dissemination, bone lesions still seeded secondary metastases in the recipient whereas mammary fat pad lesions did not. To analyze phylogenetic relationships between bone lesions and subsequently formed metastases, an evolving barcode system was used that revealed parent–child relationships between primary and secondary metastases, showing that metastases could seed other metastases. Importantly, the dissemination was able to occur from small lesions. When single cell–derived progeny of human breast cancer cells were injected into various organs to form tumors and extracted from mice after several weeks, bone-entrained cancer cells were more metastatic than mammary fat pad– or lung-entrained cancer cells, showed reduced organotropism, and displayed ALDH1 activity and CD44 expression, two markers of stemness. These bone-entrained phenotypes were reversible, indicating a mechanism independent of genetic selection. Bone-entrained cancer cells exhibited high EZH2 activity, and pharmacologic or genetic inhibition of EZH2 significantly reduced secondary metastases. In summary, this work reveals that the bone microenvironment, through EZH2-mediated reprogramming, enhances further spread of metastases to multiple organs. ■

Zhang W, Bado IL, Hu J, Wan Y-W, Wu L, Wang H, et al. The bone microenvironment invigorates metastatic seeds for further dissemination. Cell 2021;184:2471–86.E20.