Varicella-Zoster Virus Infection and Brivudine Therapy: Unexpected Response in Sarcoma Patient

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Abstract
Soft tissue sarcoma is a heterogeneous disease and treatment options are limited in advanced stage settings. Brivudine is a thymidine-nucleoside analog and inhibits DNA polymerase in VZV infection. We demonstrated a case of a patient who was diagnosed with both VZV infection and advanced stage sarcoma, and unexpected anti-tumoral response after brivudine therapy.

Keywords: VZV-infection, brivudine, undifferentiated pleomorphic sarcoma, anti-tumoral response

Case Report
An 81-year-old male patient was diagnosed with undifferentiated pleomorphic sarcoma of the lesion located left upper chest wall and bilateral pleural metastasis. Laboratory findings were within normal limits. Physical examination revealed a yellowish lesion with surrounding erythema. The patient was commenced on brivudine therapy, which resulted in a remarkable response to sarcoma lesions. The patient is currently under ongoing treatment for sarcoma and VZV infection.

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revealed about 1 cm solid mass on the right anterior chest wall and about 2.5 cm mass on periumbilical region. On the other hand, he suffered from zona lesions located on the right neck and chest wall including a mass lesion. Biopsy was consulted to our soft tissue sarcoma experienced pathologist and confirmed it as undifferentiated pleomorphic sarcoma. In order to stage the disease, CT imagings were ordered.

Figure 1 shows initial thorax tomography which demonstrates mass on the left anterior chest wall and pleural metastasis on bilateral locations. The patient was consulted to the medical oncology department and admitted to us 2 weeks later, his PET/CT imaging demonstrated disease progression (Fig. 1). Then, the patient had VZV – zona –infection and consulted to dermatology. He received brivudine for VZV infection. We advised the patient to admit to oncology outpatient after VZV infection therapy. After 4 weeks, surprisingly, a remarkable response to brivudine was inspected through physical examination, and thorax and abdomen CT imagings showed a nearly completed response (Fig. 2a and 2b). We did not give any chemotherapy or cytotoxic agent against UPS lesions.

We advised only monitoring with active follow-up. Unfortunately, he did not continue to follow up later. After 27 months, his last visit was due to pneumonia, and died in the intensive care unit. The last thorax CT imaging showed disease recurrences on bilateral pleural surfaces (Fig. 3).

Discussion

We report the case of a patient with newly-diagnosed both UPS and a VZV infection, who was treated with brivudine and had a remarkable and unexpected objective response of tumoral lesions to brivudine therapy.
Nucleoside analogs are used in the treatment of viral infections or cancer. Inhibition of DNA replication by depleting deoxyribonucleotide synthesis leads to cell growth arrest or cell death. For instance, inhibition of thymidylate synthase and ribonucleotide reductase impairs DNA replication by structurally modified nucleoside analogs are used in the treatment of cancer cells. On the other hand, thymidine kinase is a DNA salvage enzyme and play role in re-generating thymidine for DNA synthesis. Apart from DNA synthesis, it has a critical role in the repair mechanisms after DNA damage. In addition, it was shown that serum human TK activity may differ between solid cancer cells regarding breast and prostate cancer cells. There is an important question about whether human TK is different than viral (herpes) TK. Although there is limited data, human TK was found to be molecularly different than viral TK. Further studies are needed to discover these molecular differences may be an option for cancer treatment. Moreover, there is new data about serum thymidine kinase levels are above in patients with soft tissue sarcoma and there is not enough data on the importance of TK activity and sarcoma pathogenesis. Current studies are now trying to identify links between TK1 and cancer pathogenesis. In addition, brivudine is an oral thymidine nucleoside analog and has greater activity against viral TK and its activity against tumor cells is unknown. Brivudine (RP101) as a potential cancer drug was shown a novel approach for the prevention of chemotheraphy resistance and enhancement of chemosensitivity in animals and pancreatic cancer patients. But later, there was no further studies in the field of oncology. Herein, we firstly demonstrated that patients with UPS who received brivudine had surprisingly near-complete responses to brivudine about 4-weeks later (Fig. 2). Further studies about brivudine and its potential role against soft tissue sarcoma are needed.

On the other hand, in the growth of cancer tissue, the tumor microenvironment establishes acquired MHC and antigen loss to escape from the immune system. By different mechanisms including viral infection, this pathway may reverse and lead to a tumor microenvironment immune flare status—from cold status to hot—and may enhance the tumor antigen-specific T cell activation and recruitment. Further studies are needed to clarify this surprising response to UPS lesions and whether this response belongs to brivudine or VZV infection-mediated T cell activation against tumor cells. Due to fact the limited therapeutic agents against soft tissue sarcoma, it will be valuable to demonstrate the potential efficacy of nucleoside analog or a potential oncolytic viral therapy agent against soft tissue sarcoma.

Disclosures

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