Synergistic Anti-Tumor Effects of Zoledronic Acid and Radiotherapy against Metastatic Hepatocellular Carcinoma

Kazuhiko Morii¹, Yuhki Aoyama¹, Shinichiro Nakamura² and Hiroaki Okushin¹

Abstract

A 72-year-old man with advanced hepatocellular carcinoma and decompensated hepatitis C virus-related cirrhosis suffered from a metastatic femoral fracture. After undergoing radiotherapy, he was only treated with supportive care, except for the administration of zoledronic acid (ZA). Thereafter, the initially elevated serum α-fetoprotein and des-gamma carboxyprothrombin levels declined to within the normal ranges. Hepatic and metastatic adrenal tumors, distant from the radiation field, exhibited a surprising regression. ZA is known to inhibit the activity of osteoclasts, bone-residential macrophages, and has been reported to have a direct anti-tumor effect. ZA may adjust the immunological milieu in tumor microenvironments by inhibiting the tumor-associated macrophages. Because radiotherapy can enhance the presentation of tumor-associated antigens, ZA and radiotherapy may exert synergistic anti-tumor effects.

Key words: hepatocellular carcinoma, tumor-associated macrophage, tumor microenvironment, zoledronic acid, radiotherapy

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Introduction

Hepatocellular carcinoma (HCC) is often diagnosed at an advanced stage, with a vast extent of hepatic and/or extrahepatic spread. Such patients are not candidates for curative therapies, including local ablation, surgical resection, or transplantation. Transarterial chemoembolization (TACE) and the administration of sorafenib may be given to selected patients. However, they cannot be administered in the patients with poor functional hepatic reserve. The life expectancy is dismal when supportive care is the only possible therapy that can be applied.

Cancer cells are surrounded by a complex microenvironment (1) which yields chronic smoldering inflammation and promotes the heightened survival of cancer cells (2, 3). Cancer progression is regulated by an evolving crosstalk between the cancer cells and the host immune system, a process known as immunoediting (4). Tumor-associated macrophages (TAMs) are at the center of the invasive cancer microenvironment (5, 6). TAMs communicate with the tumor cells, facilitate tumor angiogenesis, extracellular matrix degradation and remodeling, and promote tumor cell motility (7). Accordingly, TAMs are potential targets for cancer therapy (8).

Zoledronic acid (ZA) is a well-tolerated drug for the treatment of bone metastasis in many types of cancers. ZA inhibits the activity of osteoclasts, bone-residential macrophages. ZA has been reported not only to reduce skeletal tumor burden but also to have a direct anti-tumor effect in certain cancers including neuroblastoma and cervical cancers (9-11). Improved outcomes on the disease-free survival were suggested in menopausal high-risk women with early breast cancer (12). ZA reportedly additionally demonstrated a direct inhibitory effect on HCC in in vitro and in vivo experiments (13). However, it has not yet been investigated whether ZA has an anti-tumor effect against human HCC. To address this question, we herein describe a patient with advanced HCC who exhibited a surprising tumor regression after ZA treatment and radiation.

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ously. The black asterisks indicate the serum HCV-RNA levels examined 9 months previously and
recently. Note the simultaneous decline of the DCP and ALT levels after the introduction of zole-
dronic acid. ALT, DCP, RFA, and TACE denote alanine aminotransferase, des-gamma carboxypro-
thrombin, radiofrequency ablation, and transarterial chemoembolization, respectively.

Case Report

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pathological fracture of the left femur 20 months previously.
The metastatic femoral involvement of HCC was detected
(Fig. 2). He was surgically treated to mend the fracture and
then received radiotherapy, with a total dose of 30 Gy. A
pathological examination of the resected bone tumor re-
vealed completely necrotic cancer tissue, which was mor-
phologically reminiscent of HCC (Fig. 3). Soon after the ra-
diotherapy, ZA treatment was initiated at a monthly dose of
3.3 mg per body. Other than the ZA treatment, he had been
solely managed with supportive therapies. Immediately prior
to the introduction of ZA, the patient’s laboratory tests re-
vealed the following: serum albumin, 2.2 g/dL; total biliru-
bin, 2.1 mg/dL; prothrombin INR, 1.65; aspartate aminotrans-
ferase, 43 U/L; alanine aminotransferase (ALT), 89 U/
L; alkaline phosphatase, 525 IU/L (reference range: 115-
359); fasting blood glucose, 115 mg/dL; glycated hemoglo-
bin, 6.9 %; serum creatinine, 1.8 mg/dL; prothrombin, 2.1
mg/dL; α-fetoprotein (AFP), 50.8 ng/mL; and des-gamma carboxyprothrombin (DCP), 28,104 mAU/mL. Abdominal magnetic resonance imaging (MRI) obtained at that time revealed a huge, right
adrenal metastatic tumor (Fig. 4) and liver lesions (Fig. 5).
Two months after the introduction of ZA, the serum levels
of AFP, DCP, and ALT began to decline. No anti-
inflammatory drugs, ursodeoxycholic acid, or glycyrrhizin
was administered. Three months after the introduction of
ZA, the patient’s AFP, DCP, and ALT levels declined to
within the normal ranges and have remained stable (Fig. 1).
It was noted that the patient’s serum HCV-RNA levels ex-
amined 9 months previously and recently were 2.8 and 0
(undetectable) log_{10} IU/mL, respectively. A recent abdominal
of the serum HCV-RNA levels was observed, however, the pretreatment viral load was unfortunately not quantified. ZA has been documented to induce the inhibition of HCV replication mediated by the activation of γδ-T cells and to restore a Th1-oriented immune response in HCV patients (25). This finding indicates a possible crosstalk between ZA and a process involved in ameliorating hepatic inflammation.

The spontaneous regression of HCC has been reported to follow ischemic insults, such as intra-peritoneal hemorrhages of HCC and upper gastrointestinal hemorrhages (26). However, no precipitating events were observed in the present case. The insufficient development of feeding vessels compared with the tumor growth rate may have evoked the spontaneous regression of HCC. Nonetheless, the simultaneous regression of both the adrenal and hepatic tumors was unlikely to be due to local perfusion insufficiencies.

The abscopal effect is a significant growth inhibition of the tumors outside the irradiated field in response to localized radiotherapy (27). The abscopal effect remains a possible cause of tumor regression in the present case. However, this phenomenon is seldom encountered and cannot always reliably be achieved. Therefore, it is unlikely to be the de facto assumption.

There are some limitations associated with the present study. We were unable to show histological evidence that TAMs were undeniably involved in the tumor tissues. The resected bone tumor consisted of entirely necrotic cancer tissue (Fig. 3). Although immune cells were presumably observed throughout the cancer cells, they were apoptotic. As such, the precise identities of the immune cells could not be determined. It would be ideal to show histological evidence of the infiltration of macrophages in the tumor microenvironment. Nonetheless, we were reluctant to perform a tumor biopsy in the present patient due to the potential risk of hemorrhaging and tumor cell seeding, which can occur in the patients with poor functional hepatic reserve.

Discussion

When the femoral fracture occurred, a poor functional hepatic and renal reserve of the present case had limited the therapeutic options to supportive care. Accordingly, radiotherapy and the administration of ZA were initiated to relieve the patient’s pain. Surprisingly, these combined treatments resulted in the unexpected regression of the tumors in the adrenal gland and the liver. This may have resulted from the synergistic anti-tumor effects of ZA and radiotherapy. Alternative possibilities were the spontaneous regression of HCC and the abscopal effect.

Radiotherapy can destroy cancer cells and enhance tumor-associated antigen presentation (14). However, radiotherapy-induced microenvironmental hypoxia also recruits proinflammatory cells, including TAMs and myeloid-derived suppressor cells (15, 16), which can impair the anti-tumor attack enacted by NK or T cells and induce regulatory T cells (17-19). Therefore, additional approaches would be necessary to overcome this immunosuppressive network that promotes tumor recurrence (20, 21). We focused on the immunomodulatory effects afforded by ZA. ZA has been shown to abrogate TAMs expressing B7-H4, B7 family inhibitory ligands, and to adjust the immunological milieu of the tumor microenvironment (22-24). Notably, the patient’s serum level of ALT declined along with the expression of tumor markers (Fig. 1). In addition, the concurrent decrease

MRI revealed a significant decrease in the right adrenal metastatic tumor (Fig. 4) and the shrinkage of the liver lesions (Fig. 5). Both the right adrenal gland and the liver were located far from the radiation field.
For future investigations, the development of supplementary markers that represent macrophage activation, instead of a histological examination, is anticipated. For instance, the serum level of soluble CD163 is a potential candidate marker representative of the proliferation of macrophages (28, 29). Further validation is required to determine whether ZA exhibits a reproducible anti-tumor effect against HCC and whether this is mediated by the recruitment of TAMs. Macrophages themselves do not harbor malignant mutations and therefore have a stable genome. As such, they are much less likely to develop drug resistance (6). This makes the inhibition of selected macrophage functions a good target for the cytostatic treatment of HCC.

In conclusion, we herein reported a patient with advanced HCC who exhibited an unexpected tumor regression after ZA treatment and radiation. ZA was well tolerated in our patient, who had a poor functional hepatic reserve and was therefore ineligible for TACE or sorafenib therapy. Co-targeting TAMs with local irradiation may be a promising strategy to complement conventional treatments.

The authors state that they have no Conflict of Interest (COI).
References