PI3K inhibitor BAY 1082439 and radium-223 dichloride decrease tumor burden and tumor-induced bone formation in an established bone metastatic prostate cancer model in mice

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INTRODUCTION

About 80% of patients with advanced prostate cancer (PCa) develop bone metastases, which cause significant morbidity, death, and a poor quality of life. Consequently, bone metastases are a major therapeutic target.

Bone metastases are the result of the interaction between cancer cells within the bone microenvironment (cancer cell-stromal cell interaction in the bone). Activation of PI3K pathway has an important role in the development of bone metastases. Studies have shown that PI3K inhibitor BAY 1082439 and radium-223 decreased tumor burden and tumor-induced pathological bone formation (Figure 1, Suva et al., 2017).

PCa cells disseminate to bone canceraigenetic breast cancer cell lines, osteoblasts, and stimulate bone remodeling. Former studies have shown that the interaction between cancer cells and bone cells results in pathologic bone formation (Figure 1, Suva et al., 2017).

RESULTS

The growth of the tumor was reduced by 67.9% (p=0.029) and 67.4% (p=0.009) in Ra-223 and PI3K/α/β inhibition compared to vehicle alone (Figure 3A). The combination of Ra-223 and PI3K/α/β inhibition showed an inhibitory effect on tumor growth as single agents and in combination (Figure 3B). The combination therapy was more efficient in the tumor-bearing tibia, Ra-223 (84.2%), PI3K/α/β inhibition (68.9%), and combination of Ra-223 and PI3K/α/β inhibition (79.1%) (Figure 3C).

Radiation of bone metastases (Ra-223/i احدية) is an alpha-emitting calcium isotope that can efficiently extravasate into targeted organs/tissues to increase therapy against bone metastases and has been approved for the treatment of prostate mesenchymal cancer with bone metastases (Kumar et al., 2015).

We have previously reported that combination therapy with PI3K inhibitor BAY 1082439 and radium-223 decreased tumor burden and tumor-induced pathological bone formation as compared to vehicle alone (Rissanen et al., 2013). The aim of this study was to investigate the effects of PI3K/α/β inhibition and Ra-223 in tumor-induced pathological bone formation in a xenograft/mixed prostate cancer bone metastatic mouse model.

Inhibition of pathological tumor-induced bone formation by PI3K/α/β, Ra-223 and the combination treatment

The tumor growth was reduced by 67.9% (p=0.029) and 67.4% (p=0.009) in Ra-223 and PI3K/α/β inhibition compared to vehicle alone (Figure 3A). The combination of Ra-223 and PI3K/α/β inhibition showed an inhibitory effect on tumor growth as single agents and in combination (Figure 3B). The combination therapy was more efficient in the tumor-bearing tibia, Ra-223 (84.2%), PI3K/α/β inhibition (68.9%), and combination of Ra-223 and PI3K/α/β inhibition (79.1%) (Figure 3C).

Inhibiton of tumor growth with PI3K/α, β, Ra-223 and the combination treatment

The tumor growth was reduced by 67.9% (p=0.029) and 67.4% (p=0.009) in Ra-223 and PI3K/α/β inhibition compared to vehicle alone (Figure 3A). The combination of Ra-223 and PI3K/α/β inhibition showed an inhibitory effect on tumor growth as single agents and in combination (Figure 3B). The combination therapy was more efficient in the tumor-bearing tibia, Ra-223 (84.2%), PI3K/α/β inhibition (68.9%), and combination of Ra-223 and PI3K/α/β inhibition (79.1%) (Figure 3C).

MATERIALS AND METHODS

LNCaP prostate cancer cells (ATCC) were inoculated into the tibia of 6-7 weeks old male Nude mice (70 mice per group). The mice were assigned to 4 groups, i.e., control group 1, Ra-223, BAY 1082439, and combination of Ra-223 and BAY 1082439. Treatments were continued for six weeks and the inhibitors were given in the following way: 1 mg/kg/vehicle (control); 3.5 mg/kg/Ra-223; 4.5 mg/kg/BAY 1082439; and 42 mg/kg/Ra-223 + BAY 1082439.

In the Ra-223 and PI3K/α inhibition combination group, tumor growth was further suppressed (tumor reduction 86%, p<0.001) and total tumor eradication was observed in 60% of the mice as measured by histology. (Figure 4A)

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KEY MESSAGES

BAY 1082439 and Ra-223 decreased tumor burden and tumor-induced pathological bone formation as monotherapies. The beneficial effects were further enhanced by the combination treatment PI3K/α inhibitor BAY 1082439 and Ra-223. Combining Ra-223 with PI3K/α inhibitor could enhance the inhibitory effects on bone metastases presumably by blocking PI3K/skeletal tumoral cell interaction (blocking nuclear PI3K-mediated activation of DNA-PK and inhibiting on direct tumor activity). Therefore, further evaluation of this promising combination therapy for the treatment of cancers with alterations in the PI3K signaling pathway and bone metastases, such as breast cancer and multiple myeloma, is warranted.

CONCLUSIONS

Both PI3K/α inhibitor BAY 1082439 and Ra-223 decreased tumor burden and tumor-induced pathological bone formation as monotherapies. The beneficial effects were further enhanced by the combination treatment PI3K/α inhibitor BAY 1082439 and Ra-223. Combining Ra-223 with PI3K/α inhibitor could enhance the inhibitory effects on bone metastases presumably by blocking PI3K/skeletal tumoral cell interaction (blocking nuclear PI3K-mediated activation of DNA-PK and inhibiting on direct tumor activity). Therefore, further evaluation of this promising combination therapy for the treatment of cancers with alterations in the PI3K signaling pathway and bone metastases, such as breast cancer and multiple myeloma, is warranted.

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REFERENCES


