Radium-223 dichloride monotherapy and combination therapy with zoledronic acid or doxurubicin improve survival in a mouse model of breast cancer bone metastasis

MI Sluminen\(^1\), JP Rissanen\(^1\), R Kääkönen\(^1\), KM Fagerlund\(^1\), E Alhoniemi\(^1\), D. Menburg\(^2\), K. Ziegelbauer\(^1\), J. Hallen\(^1\), SM Kääkönen\(^1\) and A Schole\(^2\)

\(^1\)Pharmatech Services Ltd, Turku, Finland 2 Global Drug Discovery, Bayer HealthCare, Berlin, Germany 3 Department of Cell Biology and Anatomy, Institute of Biomedicine, University of Turku, Finland

SUMMARY

Animals treated with radium-223 dichloride (alone or in combination with zoledronic acid) had increased survival time on day 24 compared to vehicle control, doxurubicin or zoledronic acid alone. (Figures 1 and 2)

Radium-223 dichloride monotherapy extended time to sacrifice (P = 0.039), unlike doxurubicin or zoledronic acid monotherapy which did not improve survival compared to the vehicle group. (Figure 3, Table 1)

Radium-223 dichloride in combination with zoledronic acid (P = 0.004) or doxurubicin (P = 0.001) extended time to sacrifice in comparison to the vehicle but did not provide additional survival benefit compared to the radium-223 dichloride monotherapy. (Figure 3, Table 1)

Treatment with radium-223 dichloride in combination with either zoledronic acid or doxorubicin did not have a negative effect on survival demonstrating that binding of both radium-223 dichloride and zoledronic acid to bone does not undermine treatment efficacy and safety in primarily osteolytic metastases.

Bone formation as measured by serum PNP was higher in the radium-223 dichloride monotherapy group (P = 0.041), lower in the zoledronic acid monotherapy group (P = 0.002) and did not differ from control in the radium-223 dichloride and zoledronic acid combination group. (Figures 6a and 7a)

Bone resorption as measured by serum TRACP6 activity was lower in both groups receiving zoledronic acid on day 21. (Figures 6b and 7b)

A 3-fold increase in the number of tumor cells with double-strand breaks in the radium-223 dichloride treated versus the vehicle control mice was observed (P < 0.001). This finding supports our previous observations that radium-223 dichloride has an inhibitory effect on both tumor cells and osteoclasts (Figures 8 and 9).

RESULTS

Body weight was maintained in both monotherapy and combination therapy groups treated with RzA-223 dichloride.

Ra23a dichloride reduced osteolytic lesion area in bone

Biomechanical markers of bone turnover

Ra23a dichloride induced double-strand breaks in cancer cells in vivo

CONCLUSIONS

Radium-223 dichloride therapy alone or in combination with doxorubicin or zoledronic acid increases survival in established breast cancer bone metastases mouse model

Radium-223 dichloride has a dual action targeting both tumor growth and osteolysis, both important players in bone metastasis development.

Our findings strongly support the development of radium-223 dichloride for the treatment of patients with bone metastatic breast cancer.