Effects of standard-of-care therapies on tumor growth, tumor-induced bone loss and bone pain in preclinical models of breast and prostate cancer bone metastasis and multiple myeloma bone disease

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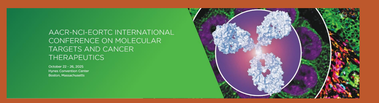


Introduction

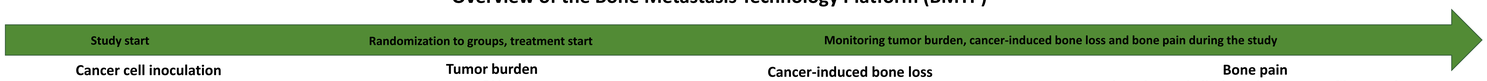
Bone metastases are a significant clinical problem in many major cancers, especially in breast and prostate cancer where 70-90% of advanced patients develop bone metastases. Myeloma bone disease is associated with similar clinical problems than bone metastases, including increased risk of fractures and bone pain that decrease the quality of life. The standard-of-care therapy (SOC) to prevent tumor growth depends on the tumor type. In this study, we demonstrate effects of SOCs in triple-negative breast cancer (TNBC) and castration-resistant prostate cancer (CRPC) bone metastasis models, and in a multiple myeloma (MM) bone disease model.

Materials and Methods

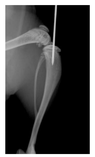
The TNBC model included 4T1 mouse triple-negative breast cancer cells in female BALB/c mice, the CRPC model included RM-1 mouse androgen-insensitive prostate cancer cells in castrated male C57BL/6 mice, and the MM model included human RPMI 8226 cells in immunodeficient female NPG mice. In all models, luciferase-labelled cancer cells were inoculated intratibially into the bone marrow to model tumor growth in bone, mimicking growth of bone metastases in patients. Tumor growth was monitored by bioluminescence imaging (BLI) and cancer-induced bone changes by X-ray imaging. Study lengths were 21, 25 and 56 days in the TNBC, CRPC and MM models, respectively. In the TNBC and CRPC models, bone pain was assessed by Von Frey filaments (mechanical allodynia). Doxorubicin (4 mg/kg, ip, BIW), docetaxel (10 mg/kg, ip, BIW) or bortezomib (0.5 mg/kg, ip, BIW) were used as SOCs in the TNBC, CRPC and MM models, respectively.

Results

Overview of the Bone Metastasis Technology Platform (BMTP)

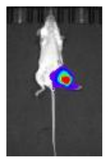


Cancer cell inoculation (Intratibial inoculation)



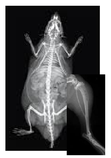
Direct injection of cancer cells to bone marrow, mimicking tumor growth in the bone microenvironment. Advantages of the intratibial inoculation include high tumor take rate and uniform tumor growth.

Tumor burden (BLI)



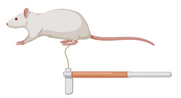
For determining tumor burden in models where tumor growth cannot be monitored by caliper. Advantages of BLI include the possibility for detection and quantitation of metastases.

Cancer-induced bone loss (X-ray imaging and scoring)



Quick and easy method for bone loss detection and monitoring during a study. Provides information on the extent of bone loss and/or drug associated bone effects.

Bone pain (Mechanical allodynia by von Frey filaments)



Non-invasive method for understanding the extent of bone pain. The measurements can be performed multiple times during a study.

TNBC bone metastasis model

In the 4T1 TNBC model, 100% of the mice had bone metastases at day 4, and maximum study duration was 21 days. Osteolytic bone lesions were clearly observed and bone pain was detected at day 7. Doxorubicin decreased tumor growth and cancer-induced bone loss but had no effect on bone pain.

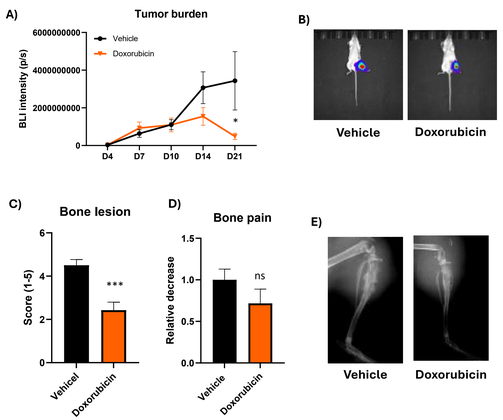


Figure 1: A) Evaluation of tumor burden by BLI for the duration of the study (mean ± SEM). B) Representative BLI images at day 21. C) Evaluation of bone loss by scoring X-ray images (mean ± SEM). D) Bone pain evaluation (mean ± SEM). E) Representative X-ray images at day 21.

CRPC bone metastasis model

In the RM-1 CRPC model, 100% of the mice had bone metastases at day 7, and maximum study duration was 28 days. Bone pain was observed at day 7, and osteolytic-mixed bone metastases were visible at day 14. Docetaxel decreased tumor growth but had no effect on cancer-induced bone loss or bone pain.

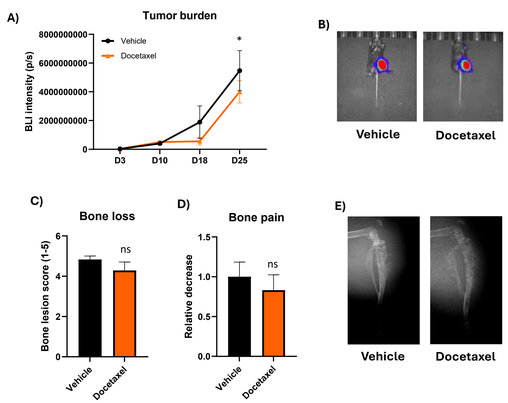


Figure 2: A) Evaluation of tumor burden by BLI for the duration of the study (mean ± SEM). B) Representative BLI images at day 25. C) Evaluation of bone loss by scoring X-ray images (mean ± SEM). D) Bone pain evaluation (mean ± SEM). E) Representative X-ray images at day 25.

MM bone disease model

In the RPMI 8226 MM model, 100% tumor take rate was detected at day 7. Osteolytic bone metastases were visible at day 21, and maximum study duration was 56 days. Bortezomib decreased tumor growth but had no effect on cancer-induced bone loss or bone pain.

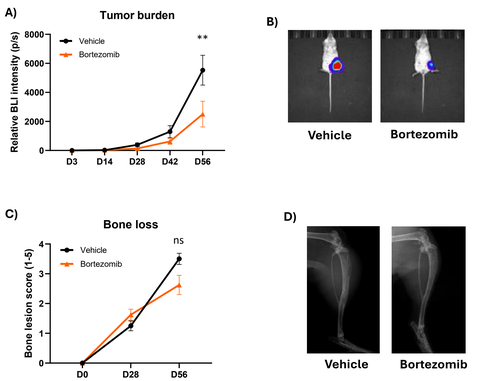


Figure 3: A) Evaluation of tumor burden by BLI for the duration of the study (mean ± SEM). B) Representative BLI images at day 56. C) Evaluation of bone loss by scoring X-ray images (mean ± SEM). D) Representative X-ray images at day 56.

Conclusions

The SOCs decreased tumor growth in all three preclinical models. Doxorubicin also decreased cancer-induced bone loss in the TNBC model. In conclusion, different SOCs have varying effects in preclinical bone metastasis models and performance of each SOC needs to be validated separately before they are included as reference compounds or used as combination partners in preclinical studies.

We conclude that BMTP is a clinically relevant translational tool showing the same clinical features that are observed in bone metastatic TNBC and CRPC or MM bone disease patients.

Doxorubicin, docetaxel and bortezomib can be used as reference compounds or potential combination partners in preclinical studies where efficacy of novel therapies on bone metastases is tested. BMTP provides a useful translational tool for evaluating efficacy of therapies on bone metastasizing cancers.

References

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