IN VIVO QUANTITATIVE IMAGING OF LUNG METASTATIC GROWTH IN A MOUSE MODEL OF OSTEOSARCOMA

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Introduction

Survival of patients with localized forms of osteosarcoma (OS) is generally above 60%. However, prognosis quickly worsens in case of metastases, which often reside in the lungs. In order to better estimate the effect of therapy, in patients with standard therapy as well as in clinical trials, it is important to collect more quantitative data on lung metastatic growth. In this study, we analyzed lung metastatic growth in vivo in an orthotopic, human xenograft mouse model of osteosarcoma that accurately reflects the human disease phenotype, using a combination of micro-computed tomographic (micro-CT) and bioluminescent imaging (BLI).

Methods

Female SCID mice were intratibially injected with luciferase/lacZ gene transduced 143B human OS cells. Lungs of mice were imaged weekly in an IVIS Lumina XR, after intravenous injection of luciferin, and once every two weeks in the Skyscan 1176 in vivo microtomography system at 35 µm voxel size. After 5 weeks, lungs were excised, Xgal-stained for lacZ expression, and photographed to analyze the amount of superficial Xgal staining as percentage of the total lung surface (%superficial Xgal staining). Next, lungs were embedded into paraffin and sectioned. Between 5-10 sections per mouse, with 400 µm space between neighboring sections, were analyzed for lung metastases using ImageJ. The percentage lung metastatic tissue derived from paraffin-embedded slides (%histology) and the %superficial Xgal staining were then compared to the percentage lung metastatic tissue as quantified from the 3D micro-CT scans, quantified using AnalyzeDirect 12.0, and the BLI signal, quantified using Living Image 4.4.

Results

Classical in vitro proliferation and migration assays showed no differences between the 143B luciferase/lacZ gene transduced cells and cells transduced with a control empty vector. Using BLI, lung metastases were detected 10 days after intratibial injection of 143B luciferase/lacZ cells. After 5 weeks, total lung metastatic volume found with micro-CT scans was on average 14% +/- 6% (mean +/- SEM), and correlated with the values found for %histology (14.5 +/- 3.5%) and %superficial Xgal staining (16.6 +/- 4.2%). The lung metastatic volume quantified by micro-CT measurements correlated equally well with BLI (r2=0.77, p=0.0089). Finally, significant correlations were found between %superficial Xgal staining and %histology (r2=0.58, p=0.04), indicating that superficial Xgal staining is a good representation of total lung metastatic load.

Conclusion

Quantitative imaging of total lung metastatic load in living mice allows us to precisely monitor in vivo growth dynamics of lung metastases. This technique can be applied to quantify treatment effects during ongoing therapy, and consequently enables us to identify treatments that most potently inhibit lung metastatic progression. The techniques used (CT) show that this principle can also be readily applied within the clinics.

Keywords : osteosarcoma, xenograft mouse model, imaging, metastasis

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