Abstract # 11215 Cisplatin ameliorates the diminished survival seen with intravenously-delivered MSCs in a murine model of osteosarcoma pulmonary micrometastasis

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Background: Mesenchymal stromal cells (MSCs) have been shown to improve bone integration between native bone and cortical allograft and aid in bone formation. They and are therefore potentially useful in limb salvage situations following sarcoma resection. MSCs have also been shown to home to and promote primary sarcoma growth when delivered intravenously or subcutaneously. We have previously reported that intravenous delivery of MSCs resulted in more rapid detection pulmonary metastasis in a mouse model of microscopic pulmonary disease following primary tumor resection.[1] While these results are concerning, it is unclear how the addition of concurrent chemotherapy, as would be commonly performed following tumor resection in a clinical patient, would alter these results.

Questions/Purposes: We endeavored to answer two principle questions: 1) Would intravenously-delivered MSCs be associated with decreased survival in mice with osteosarcoma pulmonary micrometastasis? 2) Would the addition of chemotherapy influence survival times in mice treated with intravenously-delivered MSCs following primary osteosarcoma resection? We hypothesized that survival times of mice treated with intravenously-delivered MSCs would be significantly different when compared to mice not treated with MSCs or mice treated with cisplatin.

Methods: Thirty-five 8 week old C3H mice had $1x10^6$ DLM8-luc-M1 cells injected into the proximal tibia. Primary tumors were confirmed by BLI expression and after 10 days the tumor-bearing limbs were amputated. Twenty-four hours after amputation 17 mice received $5X10^5$ adipose-derived MSCs via tail vein injection and 18 mice received no MSCs. To assess the influence of cisplatin chemotherapy on survival the mice were assigned to the following treatment groups: no treatment (n=8), MSCs alone (n=8) cisplatin alone (n=10), MSCs and cisplatin (n=11). Cisplatin was administered at 8mg/kg IP for doses one week apart beginning 24 hours after amputation and 3 hours after MSC delivery. Kaplan-Meier and Mantel Cox Regression was utilized to determine differences in survival. A p-value <0.05 was considered significant.

Results: Survival curves were significantly different when comparing cisplatin-treated, cisplatin and MSC-treated, mice treated with MSCs alone and untreated mice ($p<0.001$). Mice treated with MSCs alone had a 73% chance of earlier death than untreated controls (2.689; 95% CI: 1.248-15.78). . Mice treated with cisplatin survived significantly longer than control mice or mice treated with MSCs, and there was no difference in survival times between mice treated with cisplatin alone and mice treated with both MSCs and cisplatin.

Conclusions: Intravenous administration of MSCs in a murine model of microscopic pulmonary metastatic osteosarcoma resulted in greater risk of early death compared to untreated mice. Survival was diminished in mice receiving MSCs alone but this effect was ameliorated when mice were treated with cisplatin in addition to the MSCs.

Clinical Relevance: These results suggest that while intravenously-delivered MSCs negatively influenced survival in this murine model of pulmonary micrometastasis, the use of chemotherapy may protect against this effect.

1 Aanstoos, M. E., Regan, D. P., Rose, R. J., Chubb, L. S. & Ehrhart, N. P. Do Mesenchymal Stromal Cells Influence Microscopic Residual or Metastatic Osteosarcoma in a Murine Model? *Clin Orthop Relat Res*, doi:10.1007/s11999-015-4362-2 (2015).

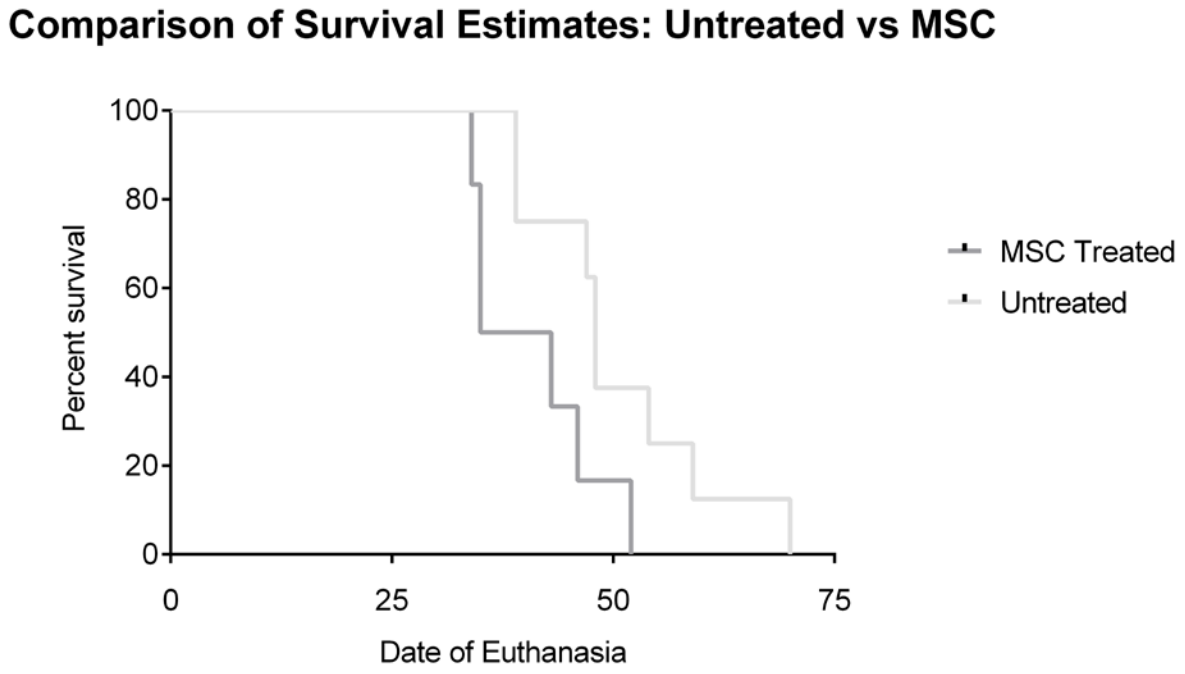

Figure 1: Kaplan Meier survival curves depicting survival of MSC treated mice versus untreated mice. Mice treated with MSCs alone (dark grey) survived significantly shorter time than untreated (no MSC) mice (light grey) (p=0.036). Mice treated with MSCS had a 73% higher risk of death compared with untreated controls.

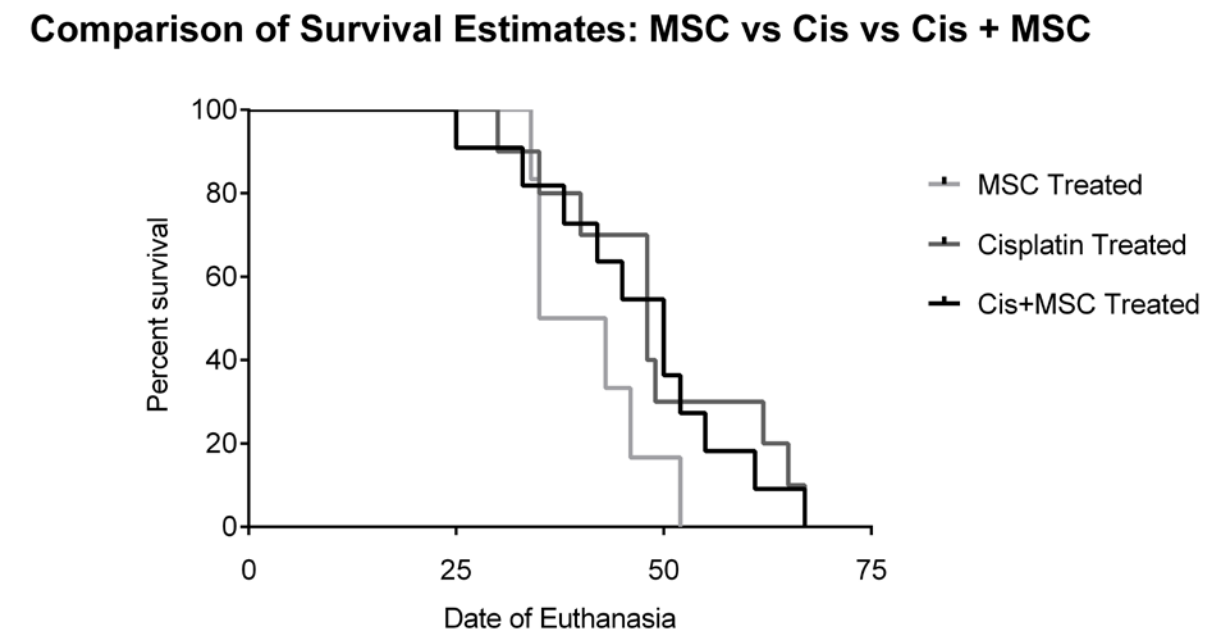

Figure 2. Kaplan Meier survival curves depicting the survival of mice treated with mesenchymal stromal cells (MSC) alone, mice treated with cisplatin (Cis), and mice treated with both MSCs and cisplatin. The survival curve of MSC alone mice was significantly shorter than cisplatin or cisplatin and MSC treatment groups ($p < 0.0001$). Survival times were not different between the two cisplatin-treated groups ($p=0.742$)