Nilotinib and lapatinib are effective for treatment of NF2 related schwannomas in the mouse xenograft model

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Introduction

Schwannomas are nerve sheath tumors that have a significant impact on patient's quality of life [1]. Surgery has been the mainstay of treatment, supplemented by radiation [2]. Unfortunately, multiple schwannomas, both peripheral and vestibular, are common in many patients, requiring systemic, rather than local therapies. Radiation therapy has been linked to malignant transformation of tumors, especially in syndromes prone for tumor development such as NF2 [3]. Many signaling pathways involved in schwannoma development and proliferation have been elucidated, and these have been the target for several suggested drug therapies [4, 5]. Bevacizumab is a vaso-endothelial growth factor inhibitor. [6]. Everolimus (RAD001) is an inhibitor of the mammalian target of rapamycin (mTOR) [7]. Lapatinib is an inhibitor of the epidermal growth factor receptor and the ErbB2 and ErbB3 downstream effector proteins [8]. Nilotinib is a tyrosine kinase inhibitor (TKI), which inhibits the BCR/ABL pathway. [9]. In this study we evaluated the in vitro and in vivo efficacy of these drugs alone and in combinations with radiation in a mouse model of human peripheral schwannoma.

Methods

The SC#4 cell line origin is mouse adult Schwann cell line from nf2-/loxP mice, second allele deleted in vitro using adeno-cre. Cells were transfected with a plasmid encoding a fusion EGFP luciferase gene under control of the CMV promoter. It is a genetically modified schwann cell linage deleted for NF2. We tested this cell line in Nu/Nu mice.

In vivo tumor implantation: After intraperitoneal anesthesia, subcutaneous implantation of the tumor in the flank was compared to tumor implantation on the sciatic nerve. For sciatic nerve implantation, Dissection through the gluteal muscles isolated the nerve. 100,000 cells were injected to the exposed nerve. For flank localization, 100,000 cells were injected in the rostral flank. In flank tumors, alternate day measurements were used to calculate volume for each measurement of each tumor. For sciatic nerve tumors, the tumors were resected and weighed after 14 days.

In vivo drug treatment: 5 days after flank tumor implantation, the mice were allocated to treatment groups Average tumor volumes for all groups were within 1 standard deviation from each other. Lapatinib, nilotinib and everolimus were gavaged, and bevacizumab injected to the tail vein.

In vivo Radiation Therapy: 5 days after flank tumor injection, the mice were allocated to similar volume treatment groups. Conformal radiation was given in different doses to the tumor. The mouse's body was shielded with lead.

In vivo Combination Radiation Therapy + Drug Treatment: 5 days after flank tumor implantaton, the mice were allocated to six treatment groups with similar tumor volume averages. The groups were: Radiation only, nilotinib only, lapatinib onlly, lapatinib and radiation, nilotinib and radiation and untreated control.

Results:

Growth of the tumors on the sciatic nerve was shown to be equivalent to tumor growth in the flank region (Figure 1). Thus we continued to use the flank tumor model for these studies looking at peripheral schwannoma growth.

Both nilotinib and lapatinib significantly decreased tumor volume as compared to the untreated control group. (Figure 2)

In vivo treatment of tumor with radiation alone yielded a consistent dose-response curve (Data not shown).

Mice treated with a single therapeutic modality: nilotinib alone, lapatinib alone, or radiation alone, all had delayed tumor growth compared to the untreated control group. The groups that received combination treatment:radiation + nilotinib or radiation + lapatinib, showed significant tumor growth delay than treatment with radiation alone. ($p<0.05$ for nilotinib+radiation vs. radiation alone; $p<0.05$ for lapatinib+radiation vs. radiation alone, Figure 3)

Conclusions

Nilotinib and lapatinib have a positive effect in this model of NF2 related peripheral schwanomma. Further research is required to evaluate whether a similar effect would be seen in the clinical setting.

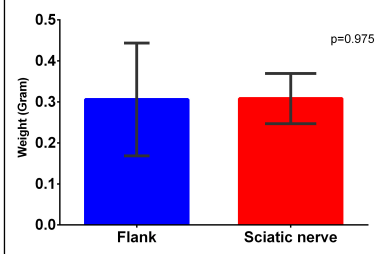
Learning Objectives

Participants should realize that nilotinib and lapatinib have a positive effect in an NF2 related peripheral schwanomma and that the effect is additive to radiation therapy.

References

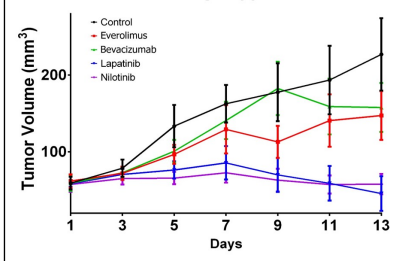
1.Evans, D.G., et al., Malignant transformation and new primary tumours after therapeutic radiation for

Figure 1



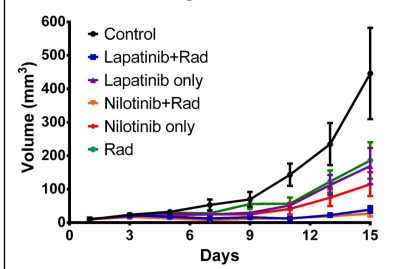
Weight of sciatic nerve tumors as compared to flank tumors

Figure 2



Tumor Volume In The Drug-only Phase

Figure 3



Tumor volume over time in the different treatment groups