PROJECT: Assessment of Intraarterial Chemotherapy in an Osteosarcoma Mouse Model of Spontaneous Metastasis

LAY SUMMARY:

OBJECTIVES: A method of intraarterial (IA) infusion using microcatheterisation of the epigastric artery of mice is developed in our laboratory. This method will allow assessing advantages of IA over intravenous (IV) chemotherapy in an established mouse model of osteosarcoma (OS) provoked by intratibial inoculation of low and high metastatic OS cell lines. The local response to IA Cisplatin as well as its effect on lung metastases will be investigated.

RATIONALE: OS is the most common primary malignant bone tumor in children and young adults. Mutliagent chemotherapy is now administered to OS patients both pre- and postsurgical resection in addition to surgical resection resulting in the 5-year survival rates of patients with OS increased by 50% compared to surgery alone. The most effective chemotherapeutic agents currently used for OS (Methotrexate, Cisplatin, Doxorubicin) are extremely toxic and have numerous undesireable side effects. There are, therefore, ongoing searches to find new agents or delivery protocols to increase tumor necrosis and decrease both side effects and occurance of metastasis. IA infusion of Cisplatin has repeatedly been reported to be effective in inducing local response in OS. Most recently, the Denver group has shown an increased 5 year survival for OS patients with localized disease using IA-IV combination chemotherapy. The therapeutic advantage of delivering Cisplatin in the main artery proximal to the tumor (i.e. femoral artery for OS of the distal femur or the proximal tibia) is presumably due to the increased first pass effect on tumor tissue which correlates with the total body clearance of Cisplatin and is inversely related to the plasma flow of the artery infused. However, the therapeutic effect, reflected by the fraction of good responders (>90% tumor necrosis) was not found to be different after IA and IV treatment. There are, therefore, controversies concerning the usefullness of this delivery method. A major drawback is the lack of a consistent in vivo model to study IA Cisplatin effect on experimental OS. Such a model will greatly help in assessing the therapeutic effect of IA Cisplatin on OS.

METHODS: The efficacy and pharmacology of IA versus IV Cisplatin delivery will be assessed. Local and systemic concentrations of Cisplatin upon IA and IV infusion will be measured. This will allow to precisely determine the dose at which IA Cisplatin should be used in this animal model. The therapeutic effect of IA Cisplatin will be assessed on low and high metastatic LacZ-tagged OS cell lines inoculated into the tibia of syngenic mice with a protocol well established in our laboratory. Local tumor and metastases in the lung and liver will be assessed both macroscopically and with histomorphometry using β-galactosidase staining of LacZ expressing tumor cells.

EXPECTED RESULTS: We expect from our proposal to shed light on the issue how efficacious IA therapy is compared to IV treatment on local tumor growth under experimental conditions. The response rate will be assessed both by the necrosis rate of the primary tumor and by monitoring the regression of the primary tumor with micro-X-rays. Moreover, we expect to understa