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Uptake of two ^{10}B-compounds in liver metastases of colorectal adenocarcinoma for extracorporeal irradiation with boron neutron capture therapy (EORTC trial 11001)

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Disseminated metastases of colorectal cancer in liver are incurable. The trial EORTC 11001 investigates whether autotransplantation after extracorporeal irradiation of the liver by boron neutron capture therapy (BNCT) might become a curative treatment option because of selective uptake of the compounds sodium mercaptoundecahydro-closo-dodecaborate (BSH) or L-*para*-boronophenylalanine (BPA). BSH (50 mg/kg bw) or BPA (100 mg/kg bw) were infused into patients who subsequently underwent resection of hepatic metastases. Blood and tissue samples were analyzed for the ^{10}B-concentration with prompt gamma ray spectroscopy (PGRS). Three patients received BSH and 3 received BPA. Adverse effects from the boron carriers did not occur. For BSH, the highest ^{10}B-concentration was observed in liver (31.5 ± 2.7 μg/g) followed by blood (24.8 ± 4.7 μg/g) and tumor (23.2 ± 2.1 μg/g) with a mean ^{10}B-concentration ratio metastasis/liver of 0.72 ± 0.07. For BPA, the highest ^{10}B-concentration was measured in metastases (12.1 ± 2.2 μg/g) followed by liver (8.5 ± 0.5 μg/g) and blood (5.8 ± 0.8 μg/g). As BPA is transported actively into cells, viable, metabolically active cells accumulate exclusively this compound. Consequently, a model is proposed to adjust the values measured by PGRS for the proportion of viable cells to express the relevant ^{10}B-concentration in the tumor cells, revealing a ^{10}B-concentration ratio metastasis/liver of 6.8 ± 1.7. In conclusion, BSH is not suitable as ^{10}B-carrier in liver metastases as the ^{10}B-concentration in liver was higher compared to metastasis. BPA accumulates in hepatic metastases to an extent that allows for extracorporeal irradiation of the liver with BNCT.

Key words: boron neutron capture therapy; autotransplantation; L-*para*-boronophenylalanine; sodium mercaptoundecahydro-*closo*-dodecaborate; ^{10}B-biodistribution

The management of hepatic metastases from colorectal carcinoma represents a significant clinical problem. The best chance of cure is achieved by complete resection of the metastases, resulting in a 5-year survival rate of 25–45%.[1,2] However, only 10–15% of all patients are eligible for surgery due to the size or number of metastases.[3] Moreover, local recurrence after surgery due to residual microscopic disease occurs in the majority of patients.[4] Although new cytostatic drugs have a response rate of around 40%, the overall survival benefit is marginal. Up to 90% of patients with liver metastases die from the disease. Thus, attention has turned to loco-regional techniques that together with surgery may be potentially curative. Procedures like cryotherapy or radiofrequency ablation can help to treat unresectable or nontotally resectable lesions but prolongation of survival is limited.[1] The use of radioactive microspheres to treat disseminated liver metastases is under investigation as a palliative modality.[5]

The future in cancer treatment is with dedicated targeted therapies, to selectively kill tumor cells whilst sparing surrounding healthy tissue, increasing efficacy and decreasing toxicity. One such option could be boron neutron capture therapy (BNCT) that provides through the limited spatial distribution of its effects a highly selective delivery of radiation.

BNCT is a targeted form of radiotherapy, which uses the ability of the isotope ^{10}B to capture thermal neutrons with high probability leading to the nuclear reaction $^{10}B(n,\alpha,\gamma)^{7}Li$. This reaction produces 478 keV photons, alpha-particles and ^{7}Li-ions, the latter 2 having a high linear energy transfer (LET) and therefore a high biological effectiveness relative to conventional irradiation. The range of these particles in tissue is 10–14 μm limiting their effects to ~1 cell diameter. This short range offers a targeted irradiation of tumor cells, if ^{10}B can be selectively delivered. BNCT has the potential to treat macroscopic tumors with high efficacy but also to kill tumor cell clusters embedded within normal tissue, whilst sparing surrounding healthy cells.

However, the success of BNCT ultimately depends upon the selective delivery of ^{10}B-atoms to tumor cells. Currently, 2 experimental drugs are available for clinical investigations:

1. Sodium mercaptoundecahydro-*closo*-dodecaborate (BSH, $Na_2{}^{10}B_{12}H_{11}SH$)[6] was designed for the treatment of tumors in the brain. It was investigated in malignant glioma[7,8] and in a phase I trial for glioblastoma multiforme (EORTC 11961).[9–11]
2. L-*para*-boronophenylalanine (BPA, $C_9H_{12}{}^{10}BNO_4$) is a derivative of the neutral amino acid phenylalanine.[12] It was used in clinical trials to treat glioblastoma and melanoma[13–15] and combined with BSH in squamous cell carcinoma of head and neck.[16,17]

Since 1986, a research program at the University of Pavia (Italy) has been underway to investigate the possibility to cure diffuse hepatic metastases by explanting the liver and irradiating the organ with BNCT followed by an autotransplantation.[18–21] Within this program, 2 patients have been treated achieving tumor remission.[22,23]

Abbreviations: BNCT, boron neutron capture therapy; BPA, L-para-boronophenylalanine; BSH, sodium mercaptoundecahydro-closo-dodecaborate; bw, body weight; conc, concentration; EORTC, european organisation for research and treatment of cancer; F, female; HFR, high flux reactor; LET, linear energy transfer; M, male; NCI CTC, common toxicity criteria of the national cancer institute; nd, not done; PGRS, prompt gamma ray spectroscopy; SD, standard deviation; y, year.

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