Medical University of Graz

TRANSPLANTATION RESEARCH

THE ROLE OF MELATONIN AND GLYCINE IN COLORECTAL CANCER LIVER METASTASES TREATMENT

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Background and Aim

Colorectal cancer (CRC) is the third most common diagnosed malignancy in men and the second in women, accounting for about 10% of all tumor types worldwide. Despite multimodal treatment strategies, clinical outcomes of advanced stage CRC patients remain relatively low. Neoadjuvant/adjuvant chemotherapy efficacy is limited due to chemoresistance, toxicity and negative side effects. Melatonin and glycine have been shown to possess anticancer and organoprotective activities. We aimed to assess the effects of melatonin and glycine supplementation on the effectiveness of chemotherapy for CRC liver metastases treatment in a rat model.

Materials and Methods

Six-week-old male Wistar rats (Janvier Labs, France), weighing approximately 200–250 g at the beginning of the experimental procedure, were maintained at the Institute for Biomedical Research at the Medical University of Graz (Austria). Four rats were housed per cage with unrestricted access to pelleted chow and tap water, and kept under controlled conditions of temperature (23 ± 1° C) and humidity (60 ± 5%) in a 12 h light/dark cycle with lights on at 6:00 AM. Animals were allowed to acclimatize for minimum of 6 days prior to the start of the experiment. CRC liver metastases were induced by implanting CC531 tumor cells (rat colon adenocarcinoma). Subsequently rats were treated with melatonin ± glycine ± FOLFOX chemptherapy for 14 days (n=180) (Figure 1). Blood parameters for liver function, μCT scan (liver and tumor volume over time), heart US (left ventricular ejection fraction over time) (Figure 2), anti-Ki67, and anti-CD31 were analysed and compared between groups. The study protocol was approved by the Austrian ministry for science, research, and economy.

Results

Glycine and melatonin treatment alone significantly reduced the tumor volume by 43.03% (p=0.044) and 63.16% (p=0,002) over time, respectively, while in the control group tumor volume increased by 8.69%. The leukocyte count at the end of experiment was significantly increased (p=0.015) in the melatonin supplemented group and this was associated with a higher count of lymphocytes. After FOLFOX application left ventricular ejection fraction significantly decreased by 9.48% in the control group. Glycine and melatonin treatment alone and their combination significantly rescued heart ejection fraction (p<0.001, p=0.013 and p=0.023, respectively).

Conclusions

For the first time the effect of melatonin alone and in combination with glycine was investigated in the model of CRC liver metastases. The results of this study suggest an inhibitory function for melatonin and glycine alone in case of liver metastases growth and beneficial properties for protection against toxic effects on heart function of FOLFOX chemotherapy.

Figure 1. Project model.

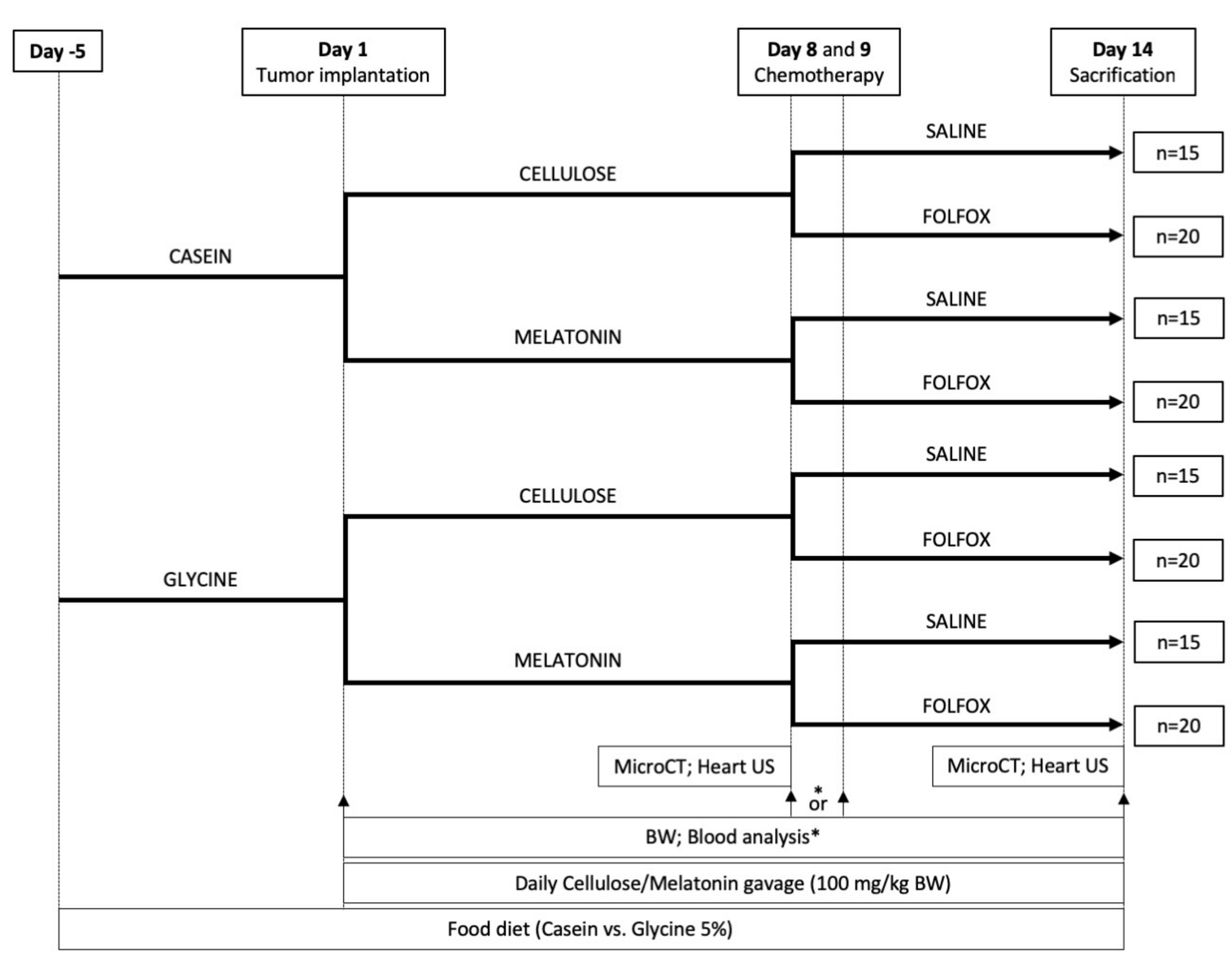
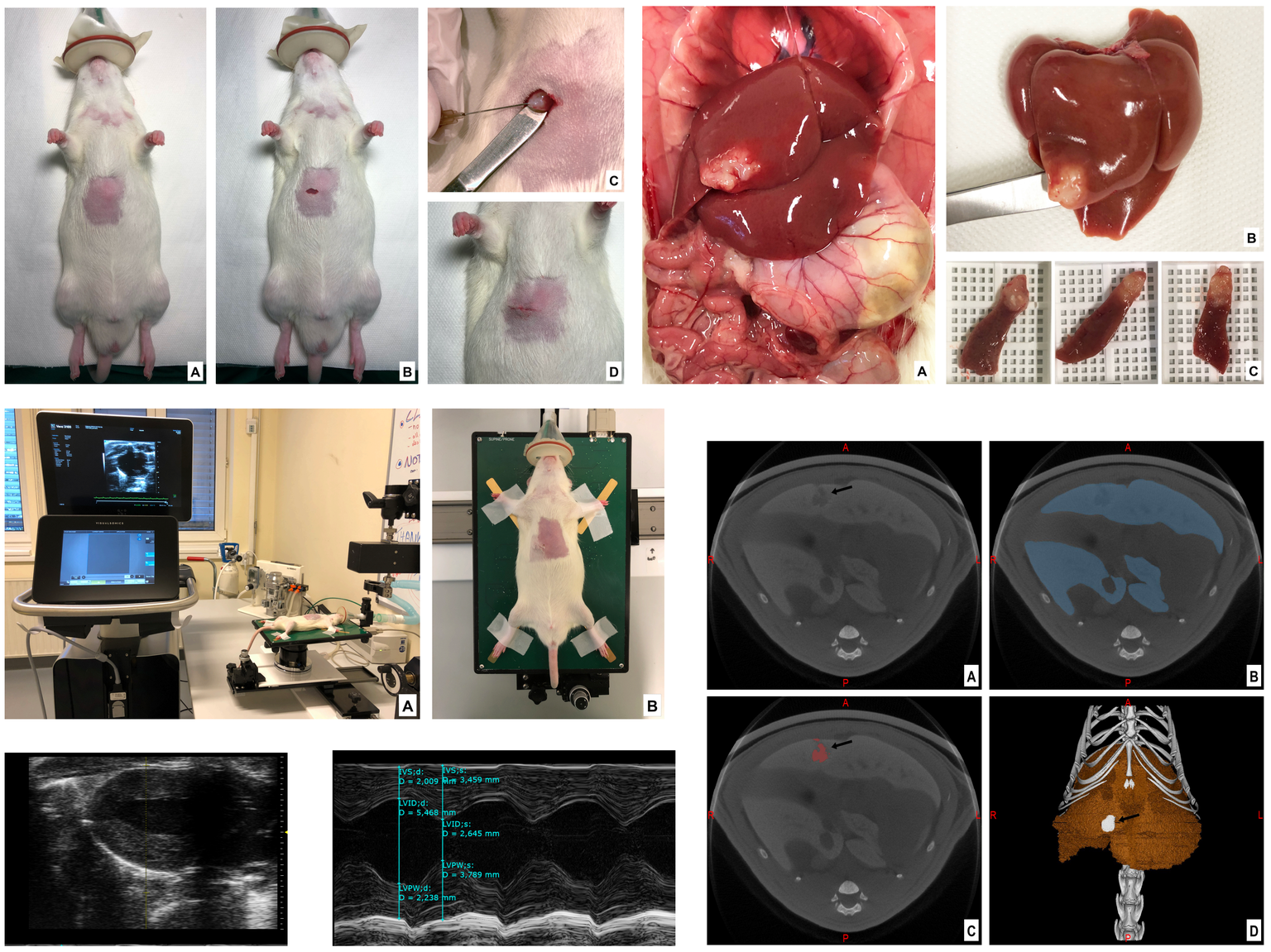


Figure 2. Tumor implantation, heart US and μCT scan.



References

Kvietkauskas M, Zitkute V, Leber B, Strupas K, Stiegler P, Schemmer P. The role of melatonin in colorectal cancer treatment: a comprehensive review. Ther Adv Med Oncol. 2020;12:1758835920931714.