Development of individualized surgical treatments for malignant melanoma

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Medicinaregatan 3, den 4 juni 13.00
av

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Avhandlingen baseras på följande delarbeten

I. Belgrano V., Katsarelias D., Mattsson J., Olofsson Bagge R. **Sentinel node for malignant melanoma: An observational study of a consecutive single centre experience.** Eur J Surg Oncol. 2019 feb;45(2):225-230

II. Belgrano V., Pettersson J., Nilsson J.A., Mattsson J., Katsarelias D., Olofsson Bagge R. **Response and toxicity of repeated isolated limb perfusion (re-ILP) for patients with in-transit metastases of malignant melanoma.** Ann Surg Oncol. 2019 Apr;26(4):1055-1062

III. Belgrano V., Mattsson J., Nilsson J.A., Olofsson Bagge R., Katsarelias D. **BRAF status as a predictive factor for response in isolated limb perfusion.** Int J Hyperthermia. 2019 Apr;36(1):511-515.

IV. Ny L., Rizzo L., Belgrano V., Karlsson J., Jespersen H., Carstam L., Olofsson Bagge R., Nilsson L.M. and Nilsson J.A. **Supporting clinical decision-making in advanced melanoma by preclinical testing in personalized immune-humanized xenograft mouse models.** Manuscript submitted.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FOR KLINISKA VETENSKAPER

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Development of individualized surgical treatments for malignant melanoma

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Background: Cutaneous melanoma is a malignancy with an increasing incidence world-wide, especially in northern Europe. The aim of this thesis is to scrutinize the results achieved by traditional surgery and the opportunities offered by translational research for the more advanced stages of the disease.

Paper I analysed outcomes of sentinel node biopsy (SNB) performed on 769 consecutive patients with cutaneous melanoma. Breslow thickness was the only predictive factor for a positive SN. The 5-year melanoma specific survival (MSS) was 81% and in multivariate analysis the negative prognostic factors for survival were SN-status, followed by Breslow thickness and ulceration.

Paper II reported on 290 consecutive patients who underwent 380 isolated limb perfusion (ILP), of which 90 were re-ILPs. The results between the 1st, the 2nd and the 3-5th were compared. Patients with a complete response at the first treatment were likely to have the same response at re-ILP without any increase in the risk for local toxicity or complications.

Paper III BRAF mutational status as a predictive factor for response was studied in 98 patients who underwent ILP. In this consecutive series, 32 patients had a BRAF V600E/K mutation and 66 patients were BRAF wild type, and no significant correlation for response or survival was found.

Paper IV was a translational study based on patient-derived xenograft models including 21 cutaneous melanoma biopsies transplanted into either NOG or IL-2 transgenic NOG (hIL2-NOG) mice. It was shown that the models reliably could be used to predict the effect of tumour-infiltrating lymphocytes against the tumours.

Conclusions: The surgical approach and therapies for patients with cutaneous melanoma are becoming more targeted and personalized. A specialised multidisciplinary approach can improve the understanding of the disease, support the decision-making process towards the most advantageous treatment options for each individual patient at a specific time.

Keywords: Melanoma, sentinel node, isolated limb perfusion, immune-humanized xenograft mouse models, translational research.