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MELANOMA AND MELANOCYTIC NAEVI

CHANGING PARADIGMS IN MELANOMA IMMUNOTHERAPY: SALMONELLA IN COMBINATION WITH DACARBAZINE AS A NOVEL APPROACH, IN A MELANOMA MURINE MODEL

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Background: Dacarbazine (DTIC) continues to be the standard of care for patients with metastatic melanoma in developing countries. As an alkylating drug, DTIC was classically considered to be cytotoxic for immune cells. However DTIC has been shown to mediate immunogenic cell death, inducing an immune response against tumors. On the other hand, Salmonella has been studied as cancer immunotherapy with proved antitumor activity.

Objective: to evaluate the potential of Salmonella Typhimurim (LVR01), as neoadjuvant therapy in combination with DTIC in a murine melanoma model.

Materials and Methods: C57BL/6 mice were subcutaneously inoculated with B16F1 melanoma cells. When tumors were palpable S. Typhimurium LVR01 was intratumorally injected and the following day, daily intraperitoneally application of DTIC was started for 3 days. Tumor volume was measured and animal survival was recorded. After 2 weeks, tumors, tumor-draining lymph nodes (TDLNs) and spleens were removed and immune response was assessed by flow cytometry, qRT-PCR and cytotoxic assay.

Results: the combination of Salmonella and DTIC retarded tumor growth and prolonged overall survival compared to control group. The combined treatment increased expressions of pro-inflammatory mRNA chemokines levels at the tumor microenviroment. Concordantly, an increase in tumor infiltrating neutrophils, NK and CD8 T cells was found. Furthermore: NK, NKT and CD8 T cells, expressed higher levels of activation and cytotoxic markers. A higher percentage of NKT and CD8 T cells were found in TDLNs of animals receiving the combined therapy. In addition, splenic NK cells from DTIC + Salmonella treated animals exhibited higher cytotoxic activity.





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Conclusion: the combined therapy induced activation of cytotoxic lymphocytes, resulting in longer survival with a safety profile. We believe that the use attenuated Salmonella as a non-specific active immunotherapy combined with standard chemotherapy in melanoma would be an interesting alternative therapeutic strategy, which could be easily moved into clinical trials.



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