

Licensing Opportunity



New topical immune modulating therapy against melanoma

- Proven effective treatment of melanoma with a combination of monobenzone and immune modifying agents
- Easy topical administration applicable in broad range of patients regardless of HLA-haplotype
- Currently phase IIa pilot study running

Therapy | Melanoma; Immune Modifying Targeted Treatment; Topical Administration

2011

Background

Melanoma is an aggressive life-threatening type of cancer that still lacks effective treatment options for metastatic disease. The incidence of melanoma in seven major markets is forecasted to increase from nearly 138,000 new cases in 2010 to 227,000 by 2019 due to continued exposure to risk factors. Some patients develop cutaneous metastases which are preferably surgically excised. In patients with large numbers of cutaneous metastases cold steel surgery no longer is an option and radiotherapy, isolated limb perfusion (ILP) carbon dioxide laser ablation, topical immune modifiers and intralesional therapy are used, often in an experimental, palliative setting. Clinical results vary; most therapies yield only temporary responses and fail to control disease. Melanoma has shown to be a good candidate for immunotherapy, during which vitiligo development has been associated with a favourable clinical outcome. We have developed a new therapy based on the potent depigmentation agent monobenzone combined with other immune modifying agents and / or immunogenic adjuvants.

The Technology

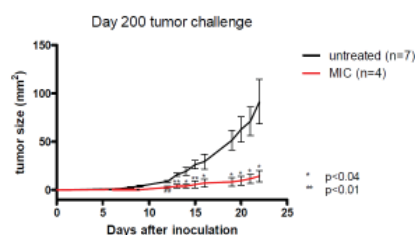
The mechanism of action of MI(C) therapy is the induction of immunity against melanocyte antigens that are shared by the melanoma cells. Monobenzone selectively interacts with tyrosinase enzyme in melanocytes, when applied to the skin. This interaction strongly increases the immunogenicity of melanocytes, resulting in specific immunity (proven in preclinical tests). During the MI therapy the immunizing ability of monobenzone is enhanced by the addition of immunostimulating adjuvant like imiquimod or CpG. Based on the shared origin of melanocytes and melanoma cells. Melanocyte-specific immunity induced MI (or MIC) therapy is also reactive against melanoma cells.

In Vitro data

Monobenzone increases melanocyte and melanoma cell immunogenicity by forming quinone-haptens to the tyrosinase protein and by inducing the release of tyrosinase- and MART-1-containing CD63+ exosomes following melanosome oxidative stress induction. Monobenzone further augments the processing and shedding of melanocyte-differentiation antigens by inducing melanosome autophagy and enhanced tyrosinase ubiquitination, ultimately activating dendritic cells, which induced cytotoxic human melanoma-reactive T cells.

In Vivo data

The therapeutic anti-melanoma effect of MI therapy was proven in the B16-B6 mouse model, showing significant growth delay of established subcutaneous B16 melanoma and prolonged survival (1). MI therapy has also been investigated in combination with an additional adjuvant CpG (MIC therapy). MIC therapy induced strong melanoma-reactive immunity, which effectively eradicated established melanoma in mice. The immune response was mediated by activated T lymphocytes, NK cells and antibodies. MIC treatment also induced a protective memory response that conferred long-term tumor-free survival, and protected against secondary tumor growth. The mice did not suffer from any side effects other than occasional development of vitiligo like patches of depigmented fur locally at the treatment site and at distant sites in long-term surviving mice. In none of the mice acute toxicity occurred.



Applications

Besides the topical treatment currently in Phase IIa pilot other treatment options for melanoma can be developed by combining different drugs. Also the possibility exists to develop a patient specific vaccine.

R&D Status

Currently a phase IIa trial is running to show proof of concept in patients. This pilot study is designed to evaluate the clinical efficacy of combined therapy with monobenzone and imiquimod cream applied directly to cutaneous melanoma metastases. Other studies in vivo with different combinations are scheduled.

Intellectual Property

Patent nr. US 11/996,753 - EU 05769178.4 - CA 2,615,710 - AU 2005334836

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Inventors

Dr. W. Westerhof, Dermatology, AMC

Dr. R.M. Luiten, Experimental Dermatology, AMC

Prof. Dr. C.J.M. Melief, Immunology, LUMC

Key publications

1. Van den Boorn JG, Konijnenberg D, Tjin EPM, Picavet DI, Meeuwenoord NJ, et al. , Effective Melanoma Immunotherapy in Mice by the Skin-Depigmenting Agent Monobenzone and the Adjuvants Imiquimod and CpG. PLoS ONE 2010, 5(5): e10626
2. Jasper G. vanden Boorn, Daisy I. Picavet, Paul F. van Swieten, Henk A. van Veen, Debby Konijnenberg, Peter A. van Veelen, Toni van Capel, Esther C. de Jong, Eric A. Reits, Jan W. Drijfhout, Jan D. Bos, Cornelis J. Melief and Rosalie M. Luiten, Skin-Depigmenting Agent Monobenzone Induces Potent T-Cell Autoimmunity Toward Pigmented Cells by Tyrosinase Haptenation and Melanosome Autophagy J Invest Dermatol. 2011 Jun;131(6):1240-51.