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Drug Targeting in Metastatic Melanoma

A Hauschild
Department of Dermatology, University of Kiel, Germany

The efficacy of current treatment modalities for stage IV melanoma patients is weak. Therefore, new treatment modalities are urgently needed. The molecular identification of therapeutic targets, which are involved in tumor progression led to the development of new agents. Among the possible targets are molecules of the signal transduction pathway since as Ras, Raf and MEK, the proteasome, histone deacetylases, methyltransferases, and melanoma-induced angiogenesis. Currently, there are numerous phase I-III trials with interesting agents and translational research programs. The most promising results were seen with Sorafenib, a multi-kinase inhibitor, in combination with Carboplatin and Paclitaxel. The US trial in 54 mainly pretreated advanced melanomas demonstrated 37% partial responses and 48% stabilized diseases. Currently, an international and a US/Canadian trial are evaluating this approach in metastatic melanoma patients. Regarding other molecules, it is unclear yet, whether they have a potential as a monotherapy or more likely as combinations with other molecules that interfere with the same pathways or alternative anti-tumor mechanisms. Among these are histone deacetylase inhibitors like MS-275 and integrin receptor inhibitors like Vitaxin (Medi-522) or CNTO-95. Another interesting approach is the augmentation of T-cell responses by the use of CTLA-4 antibodies, which inhibit regulatory T-lymphocytes. Early trials demonstrated efficacy particularly in patients, who developed autoimmune phenomenons during treatment. Phase III trials using CTLA-4 antibodies alone, combined with vaccination or Dacarbazine are underway.In conclusion, several different treatment approaches are currently under evaluation, which have in principal the capacity to define better standards of care.

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Interleukin-2 Based Adjuvant Immuno-Therapy for Melanoma Patients

L Bianchi
Department of Dermatology, Tor Vergata University of Rome, Rome, Italy

Reports of spontaneous disease regression in melanoma and its immunogenic behaviour have currently supported immuno-therapeutic approaches based on cytokines, vaccines, monoclonal antibodies, gene therapy. Interleukin-2 (IL-2) is a lymphokine with a central role in immune regulation. It activates cytotoxic lymphocytes, stimulates secondary cytokines, activates natural killer cells and macrophages, activates B-cells, induces release of hormones and activates complement factors. IL-2 was described to be efficient in stage IV melanoma as single agent, combined with chemotherapy or with immunologically active cells. Initial studies showed a response rate of 15-20% and a complete response rate of ~6% with a very small chance of long-term remission. Randomised clinical trials failed to demonstrate a convincing evidence that adding IFN-a to IL-2 was beneficial. Phase II–III studies of IL-2 based immunochemotherapy indicated durable complete response in a small fraction of patients. Nevertheless, a defined treatment schedule for IL-2-based therapy in metastatic melanoma remains debated. Furthermore, the increasingly accurate melanoma staging led to better identify patients with sufficiently high-risk of relapse. In this purpose, intermittent low-dose subcutaneous IL-2 in adjuvant post-surgery and/or after chemotherapy has been investigate to reduce the risk of disease relapse and prolong disease-free survival. The follow-up and adverse events in 7 high-risk patients (stage IB, IIA, IIC, IIII), 2/7 treated with intravenous dacarbazine (750 mg/mq on day 1, monthly) and subcutaneous IL-2 (6 million units on day 2–5, 16–19, monthly), 5/7 with subcutaneous IL-2, as single agent (3 million units on day 1–5, 8–12, monthly), are reported and discussed.

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Critical Questions in Melanoma Biological Immunotherapy Development?

B Dreno
Department of Skin Oncology, Nantes, France

Biological immunotherapy is represented by Tumor infiltrating Lymphocytes (TIL: i.e. injection of T lymphocytes generated and selected ex-vivo from blood or from the tumor) which is adoptive immunotherapy. At the clinical level, previously it has been shown that TIL were able to induce a regression of metastatic lesion (mean 30%) but without increase the overall survival (quick relapse). Recently five crucial points have been identified for the efficacy of this biological immunotherapy

1- The tumour burden

A strong interaction exists between TIL used as adjuvant therapy in melanoma stage III (AJCC) and the number of invaded lymph nodes. Indeed, the injection of TIL in patients with only one invaded lymph node was associated with an increased relapse free survival and an overall survival;

2- Migration of TIL to the metastatic stage

Four papers, now with an immunological follow-up have shown the correlation between the therapeutic benefit and the survival and the preferential migration of specific T lymphocytes to the tumor sites.

3- The specific TIL against melanoma antigens

The therapeutic benefit is directly related to the percentage of tumor antigen specific T lymphocytes, against melanoma obtained in the expansion.

4- The melanoma antigens

Recent results strongly suggest that the infusion of reactive Melan-A/MART-1 specific lymphocytes was associated with clinical efficiency of TIL treatment. Furthermore, the amount of such lymphocytes seemed to be critical for patients bearing more than one invaded lymph nodes before the treatment.

5- The mechanisms of escape to adoptive immunotherapy

Three mechanisms could decrease the efficacy of adoptive immunotherapy:

T reg cells (CD4 + CD25 + Fox p3) presents in the final expansion injected to the patient

Suppressive cytokines secreted in situ by tumor cells (IL-10, TGFβ….)

Decrease expression of melanoma expression by tumor cells

Studies are on going to try to answer to this last crucial question.

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Future Directions of Multimodality Treatment in Melanoma

C Garbe
Division of Dermatooncology, Department of Dermatology, Eberhard Karls University, Tübingen, Germany

Malignant melanoma is known as one of the tumors with most effective treatment resistance mechanisms among all cancers. Drug resistance to chemotherapeutics results in low response rates of about 10 % in monochemotherapy and up to 20 % in polychemotherapy. It is still unknown whether drug targeting in melanoma will substantially increase treatment responses. Therefore, there is an urgent need for integration of additional treatment modalities into the therapeutic strategy in metastasized melanoma. First, the indication for surgical metastasectomy has to be checked in all melanoma patients with distant metastases. New imaging techniques provide a more complete picture of the pattern of metastases and enable surgical resection also in multiple organs. Resection of visceral metastases has to be considered particularly in metastases of brain, lung, liver and bone. Radiotherapy is an effective option in metastases of the brain, bones and soft tissue. Its effect can be enhanced particularly in soft tissue by hyperthermia. Finally, the role of vaccination treatments has to be defined in relationship to chemotherapy and targeted therapies. Vaccination therapies may become particularly an option in patients after surgical metastasectomy. Intelligent strategic combinations of treatment modalities are warranted in order to prolong patient survival in the stage of distant metastases.

Drugs used to treat Melanoma, Metastatic. The following list of medications are in some way related to, or used in the treatment of this condition. Select drug class. All drug classes alkylating agents (2) miscellaneous antineoplastics (5) miscellaneous uncategorized agents (1) antineoplastic interferons (3) antiviral interferons (3) multikinase inhibitors (12) anti-CTLA-4 monoclonal antibodies (2) interleukins (2) anti-PD-1 monoclonal antibodies (4). Rx. OTC. Off-label. Only Generics. Drug name. Rating. Reviews. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature 467, 596â€“599 (2010). CAS Article Google Scholar.Â Cite this article. Flemming, A. Targeting mutant BRAF in metastatic melanoma. Nat Rev Drug Discov 9, 841 (2010). https://doi.org/10.1038/nrd3304. Download citation. Published: 29 October 2010. Although metastatic melanoma is not easy to treat, you do have options. Choosing what's right for you will depend on where and how big the cancer is, what your health is like, and what your wishes are. Since most cases of metastatic melanoma can't be cured, the goals of treatment are to: Shrink or stop the growth of the disease where it has spread. Stop it from spreading to new areas.Â American Cancer Society: "Melanoma Skin Cancer Overview," "Treatment of melanoma sin cancer by stage,â€ "Targeted therapy for melanoma skin cancer." Cancer Research UK: "Living with Advanced Melanoma." FDA: "FDA approves Yervoy to reduce the risk of melanoma returning after surgery," "FDA approves Cotellic as part of combination treatment for advanced melanoma."