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Systemic treatment of metastatic malignant melanoma

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Chemotherapy: Systemic therapy for melanoma, both as adjuvant therapy and for treatment of disseminated (stage IV) disease, remains unsatisfactory. Patients with high-risk or metastatic disease should be considered for enrollment in investigational studies. Few chemotherapeutic agents have demonstrated antitumor activity against metastatic melanoma. In a review of phase II trials, only 4 of 30 drugs that were tested demonstrated a response rate greater than 18% in melanoma patients. The best-studied single agents for treatment of melanoma are Dacarbazine (D) (20% RR), Fotemustine (F) (24% RR), Vindesine (V) (14% RR) and Cisplatin (P) (23% RR).

Combination: The role of combination chemotherapy in treatment of advanced melanoma is not entirely clear. The most active combination regimens (FDV) (32% RR) and (PDV) (32% RR).

Biologic therapy: There is evidence that the immune system can influence the pathogenesis of melanoma. Several biologic agents have been tested in patients with metastatic melanoma and have demonstrated antitumor activity. Interferon α (16% RR) and Interleukine 2 (18% RR).

Combinations of biologic agents and chemotherapy: Exploration of combinations of biological agents and chemotherapy for treatment of melanoma is an active area of investigation. Preclinical studies on animals have suggested that combinations of recombinant cytokines or monoclonal antibodies (e.g. IL2 and Interferon α, monoclonal antibody and IL2, tumor necrosis factor and Interferon γ) are additive or synergistic. Clinical trials of cytokines with chemotherapy have been initiated and have shown promising results (45–50% RR) with some 5 to 10% long term unmaintained remissions.

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T cell recognition of melanoma-derived antigens: Implication for peptide based immunotherapy

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A high number of T cell-recognized epitopes expressed on melanoma cells has been recently identified. However, it is still unclear which antigen could be effective in mediating a significant anti-tumor response when used as a vaccine. Preliminary studies showed that immunization of melanoma patients with epitopes derived from proteins of the MAGE family (whose systemic immunogenicity, i.e. the ability of inducing specific CTL in peripheral blood of melanoma patients after *in vitro* culture, is apparently low) may result in significant clinical responses. On the other hand, no major tumor regression could be observed when patients were vaccinated with epitopes derived from the differentiation antigen MART-1/Melan A, an antigen that has been shown to be the most immunogenic in HLA-A2.1 melanoma patients. It is thus crucial to identify the mechanisms responsible for the failure of some antigens to mediate a significant anti-tumor response *in vivo*. One of these mechanisms has been recently identified as related to the existence of natural analogs of the MART-1 immodominant epitope in normal human proteins other than MART-1. These analogs exert a partial agonist/antagonist activity on MART-1-specific CTL, thus possibly playing a role in down modulating *in vivo* anti-melanoma CTL reactivities.

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On the molecular genetics of malignant melanoma

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Cutaneous malignant melanoma in its hereditary form is involved in 5–10% of all melanoma cases. Genetic linkage analyses have revealed loci on chromosomes 1 and 9 as probable locations for genes responsible for the hereditary increased risk of malignant melanoma. Important steps forward were the localization of the CDKN2A gene to chromosome 9p21 and the obtained evidence of its involvement in the etiology of melanoma. CDKN2A germline mutations in American melanoma prone families have been linked to the development of the disease. In a large series of Swedish melanoma families the mutated gene was found in about 10% of the kindres. The CDKN2A gene product p16 has a regulatory effect on the cell cycle by interacting with cyclin dependent kinases. The product of a second gene, CDKN2B, on chromosome 9p21, has a similar function but no germline mutations have been observed. Both CDKN2A and CDKN2B mutations have, however, been observed in sporadic melanoma tumors. Other genes involved in the regulation of the cell cycle are at present studied. A germline mutation in the CDK4 gene have been registered in two American melanoma families. Molecular genetic studies of sporadic melanoma point at several cell cycle regulation control genes as possible targets for inherited DNA alterations predisposing for melanoma. Whether additional genes with functions in other pathways are involved in melanoma genetics remains to be determined.

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Regional therapy for melanoma: Randomised trials

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A phase III study-EORTC 18832 and WHO Melanoma CT n°15 – on the value of prophylactic Isolated Limb Perfusion with melphalan (M-ILP) for >1.5 mm melanoma entered 832 evaluable (ev) pts from 17 centers. Median follow up is 6.4 years. There was a trend for longer DFI after ILP. The difference is significant if the pts with no ELND are separately analysed, with a high significance in the 1.5–3 mm thickness subgroup The impact of ILP was clearly on the occurrence of in transit metastases (ITM) which were reduced from 6.6% to 2.2%. There was no benefit of ILP in terms of survival.

In advanced melanoma of the limbs, ILP with melphalan combined with rTNFα and IFNγ (TIM-LP) gives 100% objective responses in in-transit melanoma mets. A prospective randomized phase II study compared 32 pts who received TIM-ILP to 32 pts who received TM-ILP (without IFN$\gamma\pi$). There was an ORR and CR rate superior with TIM over TM -100% vs 91% and 78% vs 69% respectively-, but the differences are not significant.

Conclusion: Prophylactic M-ILP cannot be recommended as as a standard adjunct to surgery in high risk primary limb melanoma. TIM-ILP or TM-ILP is a regional therapy with very high regional response rate on melanoma in-transit mets.

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Targeted immunotherapy: Dendritic cells to present tumor-associated antigens

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Dendritic cells (DC) are thought key regulators in immune responses. In particular DC, because of their efficient antigen uptake and processing machinery and their high expression of MHC class I and class II molecules, are well equipped to stimulate naive lymphocytes. Until recently, the extremely low abundance of DC in the circulation has hampered the study of these antigen presenting cells. Recently, several studies have demonstrated that it is possible to obtain DC from bone marrow or from peripheral blood monocytes after in vitro culture with cytokines. In particular GM-CSF and IL4 are frequently used. These immature DC can be further differentiated into mature DC using cytokines like TNF or IL-1. These cells express high levels of MHC molecules, and also CD80, CD83, and CD86. We and others were capable, using these DC as antigen presenting cells, to induce primary immune responses against melanocyte differentiation antigens. Thus we obtained several CTL from blood of healthy donors as well as from melanoma patients that recognize melanocyte differentiation antigens. These findings demonstrate that DC may be powerful immunogens and several strategies to use DC to treat cancer patients have recently been developed. These not only include the injection of DC loaded with peptides or proteins derived from tumor associated antigens, but also DC transduced with RNA or DNA encoding such proteins may be considered.

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Surgery: Still the gold standard?

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Surgery as primary treatment for cancer of the oesophagus and gastro-oesophageal junction today is challenged by a variety of multi-modality regimens. Several groups, including our own, however have continued to advocate radical resection and extended lymphadenectomy as the primary