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Novel treatment strategies for malignant melanoma: A new beginning?

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Abstract

Malignant melanoma is one of the most common cancer types among the Caucasian population. While the prognosis is excellent for patients diagnosed at an early stage and treated by adequate surgery, unresectable or advanced metastatic diseases shrink the overall survival at 5 years dramatically to less than 10%. For disseminated malignant melanoma, the appropriate systemic medical treatment is still controversial. Fortunately, progress in the molecular biology and in the understanding of pathogenesis has been made recently and should in the near future translate into molecular-based therapeutic strategies.

In this review, we briefly describe the status of current treatment strategies and existing standards for malignant melanoma. We will focus on the new and emerging compounds including recent developments of targeted therapy such as antiangiogenic and immunomodulatory drugs, Bcl-2 antisense therapy, raf kinase inhibitors, heat shock protein modulators, anti-cytotoxic T lymphocyte-associated antigen (CTLA)-4 monoclonal antibody and finally PARP and proteasome inhibitors.

Keywords: Malignant melanoma; New treatment strategies; Molecular targeted therapies

1. Introduction

Malignant melanoma is the most aggressive form of skin cancer causing the majority of deaths, which is on the rise in western populations. During the past few decades, the incidence of cutaneous melanoma has been rising in both sexes in almost all developed countries [1]. In Scotland, for example, between 1979 and 1998 the incidence in men increased by 303%, from 3.5 to 10.6 per 100,000, and that in women by 187%, from 7.0 to 13.1 per 100,000 [2]. The prognosis of malignant melanoma is strongly related to the stage at which it is detected: patients with early diagnosed and surgically excised tumours have a high probability of complete cure [3,4]. However, the 5-year survival for patients with spread of disease to regional lymph nodes is only 54%

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[5], for patients with disseminated melanoma the prognosis is extremely poor with a 5-year survival of about 6% and a median survival duration of 7.5 months [6,7] despite a variety of therapeutical efforts that have been made.

Melanoma progression is well defined in its clinical, histopathological and biological aspects, but the molecular mechanism involved and the genetic markers associated to metastatic dissemination are only beginning to be defined. The recent development of high-throughput technologies aimed at global molecular profiling found previously unknown candidate genes being involved in melanoma, such as WNT5A and BRAF. In fact, several tumour suppressors and oncogenes have been shown to be involved in melanoma pathogenesis, including CDKN2A, PTEN, TP53, RAS and MYC, though they have not been related to melanoma subtypes or validated as prognostic markers. Moreover, correlations between molecular biology and survival data have been detected recently. For example, there is strong evidence that there is an association between polymerase chain reaction-based measurements of tyrosinase mRNA in peripheral blood and disease-specific survival time in melanoma patients [8]. The oncogene *Akt* is a serine/threonine kinase leading to stimulation of cell cycle progression, cell proliferation and inhibition of apoptosis that has been investigated in melanoma pathogenesis. The expression of *Akt* increases with melanoma invasion and progression and is inversely correlated with patient survival serving as an independent prognostic marker [9].

2. Current status in systemic therapy

The appropriate systemic treatment for disseminated melanoma is still a matter of discussion and there are no defined and generally accepted standards. Single-agent therapy with dacarbazine has been the reference treatment for melanoma in several randomised clinical trials. However, only temporary clinical responses but no improvement of patients' overall survival could be achieved [10,11]. Temozolomide is now studied in many trials as first line therapy. Patients are treated very differently in different clinical centres, patients will be given mono-chemotherapy, polychemotherapy, combined therapy with cytokines, or complex schemes with up to five different drugs. Furthermore, many patients are treated in experimental trials. Eigentler et al. [12] have excellently reviewed the palliative treatment of disseminated melanoma. For both, clinicians and patients, the current situation is complex and unsatisfactory.

Therapeutic strategies include chemotherapy, bio chemotherapy, immune adjuvants, cancer-specific vaccines, cytokines, monoclonal antibodies and specific immunostimulants. However, the only FDA-approved immunological approach in this disease in the last 30 years has been high-dose IFN-α and high-dose bolus IL-2 in the metastatic treatment setting, but only a minority of patients benefit from this treatment in terms of long-term survival. Moreover, both agents are associated with high costs and toxicity rates [13]. It is obvious that there is a need to develop new and innovative treatment options. The most promising approaches are: antiangiogenic and immunomodulatory drugs, Bcl-2 antisense therapy, v-raf murine sarcoma viral oncogene homologue B1 (BRAF) and heat shock protein modulators, and finally anti-cytotoxic T lymphocyte-associated protein (CTLA)-4 monoclonal antibody will be discussed in this review.

3. Novel treatment strategies

3.1. Antiangiogenic and immunomodulatory drugs

Thalidomide was one of the first drugs demonstrating antiangiogenic and immunomodulatory effects. It has been introduced in the 1960s for the treatment of morning sickness in pregnant women. Due to reports of teratogenicity it was withdrawn until its renaissance in the 1990s. Interestingly, it was found that this complication was caused by the antiangiogenic property of thalidomide by inhibition of blood vessel growth in the foetus. Thalidomide inhibits the basic fibroblast growth factor (bFGF) as well as the vascular endothelial growth factor (VEGF) [14]. Other immunomodulatory effects are mediated over the inhibition of NF-κB [15], the alterations of $CD8^+$ and $CD4^+$ T cell function, the stimulation of cytokine production of IL-2 and IFN-γ as well as the inhibition of other cytokines such as IL-6 and IL-12 [16].

Multiple studies have confirmed the activity of thalidomide in multiple myeloma. However, the activity of thalidomide in solid tumours is less prominent. The most promising results have been reported in renal cell cancer [17], Kaposi's sarcoma, prostate cancer, high-grade glioblastoma and malignant melanoma [18].

Although thalidomide as monotherapy has neglectable efficacy with no objective response in patients with advanced malignant melanoma [19–21], the combination especially with temozolomide has shown improved efficacy in metastatic melanoma. In a phase II trial with 38 patients combining temozolomide 75 mg/(m^2 day) with thalidomide 100–400 mg daily a response rate of 32% (1 complete response (CR), 11 partial responses (PR), 7 stable diseases (SD)) could be demonstrated with a median survival time of 9.5 months [22]. Recently, the same group published a phase II study with 26 patients using the same combination therapy of temozolomide and thalidomide in patients with brain metastases from melanoma and could demonstrate that the combination was an active oral regimen in these patients [23]. Another phase II study compared the combination of temozolomide with either IFN-α or thalidomide in 181 patients and could demonstrate a response or disease stabilisation in 25% of patients receiving the temozolomide plus thalidomide combination [24]. For further investigations and subsequent phase III studies, the thalidomide–temozolomide combination is an appealing treatment option.