Adjuvant treatment for high risk melanoma. Where are we now?

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Abstract The survival rate for stage 3 and 4 melanoma is very poor. In the absence of effective treatments for metastatic disease focus has shifted to the adjuvant setting. While we are now able to identify those who are at high risk of recurrence the role of adjuvant systemic treatment in these individuals is still undefined. This is partly due to the lack of effective treatments, despite the advances in the understanding of the biology of melanoma and the natural history of the disease process. Of the various treatments studied in the adjuvant setting only interferons and vaccines have been shown to affect the clinical outcome but no agent has been accepted as a standard, with differences in practice between the US and Europe. In this review article we will report what is known at this time about the different agents studied in the adjuvant setting and refer to some new areas of research that may play a bigger role in the future management of melanoma.

Keywords Melanoma · Adjuvant · Radiotherapy · Vaccines · Interferon

Introduction

The incidence of cutaneous melanoma is increasing throughout the world by 5% per year [1]. However, due to increased awareness, cutaneous melanomas are being diagnosed at an earlier stage and as a result the mortality rate has begun to plateau. Melanoma can have a more variable and unpredictable outcome than almost any other malignancy. The disease is relatively resistant to current therapeutic agents and thus considerable research is being conducted into finding alternatives. To date surgical resection still offers the best chance of cure. Adjuvant therapy should be considered for patients with high risk of recurrence, particularly those with thick primary tumors and/or positive lymph nodes.

Although melanoma is far less common than other skin cancers, it is the major cause of death from skin cancer and is more likely to be accurately reported and diagnosed than other skin cancers. They most commonly develop on sun-exposed areas, on the back in males and the lower legs in females. The most important prognostic factor for melanoma is the presence or absence of lymph node metastases [2]. The presence of lymph node metastases decreases
the 5-year survival of patients by approximately 40% as compared with those who have no evidence of nodal metastases [3]. The role of adjuvant systemic treatment to treat micrometastatic disease in high risk primary and resected melanoma is yet to be fully explored. In applying the principles of adjuvant therapy to melanoma, parallels should be drawn with solid tumors such as breast and colon cancer, where adjuvant chemo and radiotherapy has been shown to have an impact upon survival.

Selection of patients for adjuvant systemic therapy

The criterion for selection of patients for adjuvant therapy is based on the thickness of the primary melanoma and lymph nodes metastasis. The 10-year survival for stage IIA is 79% dropping to as low as 28% when regional lymph nodes are involved [4].


1) Patients with primary melanoma 4 mm or thicker (Stage IIB & IIC)
2) Melanoma with regional node involvement (Stage III)
3) Patients with melanoma with Breslow thickness 1.5–4 mm, physician’s discretion.

Patients at intermediate or high risk of recurrence should be referred to a specialist center, staged and considered for a trial of adjuvant treatment without any delay.

Adjuvant therapy

Currently there is no standard systemic therapy for patients with melanoma in the adjuvant setting and as such patients should be offered entry into clinical trials wherever possible. In this review article we will report what is known at this time about the different agents studied in the adjuvant setting and refer to some new areas of research that may play a bigger role in the future management of melanoma. Of the various treatments studied in the adjuvant setting only interferons and vaccines have been shown to affect the clinical outcome. Currently interferon is approved for use in the United States in the adjuvant setting, but because results from the European trials were less convincing it is not standard practice in the UK.

Biological therapy

The observations of regression of primary melanomas associated with lymphoid infiltration have led researchers to believe that immunotherapy might be effective in patients with melanoma [6]. Numerous studies have reported laboratory evidence of antibody and T cell responses to melanoma, and adoptive transfer of tumor infiltrating lymphocytes has been associated with regression of melanoma [7]. Complete spontaneous regression of melanoma has been observed in some patients, a phenomenon thought to be mediated by the immune system [8].

In the last decade, the activity of high dose interleukin-2 in producing durable complete remission and advances in supportive care that have made its administration possible have led to the widespread use of such combinations and to claims of higher levels of activity compared with less aggressive regimens. Although initial reports of phase II studies of biochemotherapy were encouraging, phase III studies did not confirm a survival benefit, and even the response rates were surprisingly low. Biological response modifiers and, more recently, vaccines are being investigated in both the metastatic and adjuvant setting. The various biological therapies studied in melanoma are interferon, interleukin 2, melanoma vaccines, Corynebacterium parvum and bacillus Calmette-Guérin.

Interferon

The interferons are a group of naturally occurring cellular cytokines with important physiological functions in antiviral and antitumor defence. Following the demonstration of IFN-alpha activity against murine B16 melanoma cell lines in vitro and in vivo, [9] clinical trials with interferon were conducted. Interferons have proved to have a biologically modifying effect on melanoma as shown in several studies, but the overall survival has been variable. The major limiting factor is the side effects.

Interferons commonly cause malaise, fevers, and flu-like symptoms. High dose interferon [10] has been shown to cause grade 3 myelosuppression in 24% of people, hepatotoxicity in 15%, and neurotoxicity in 28%. With low dose interferon [11] 10% of patients suffered significant toxicity.

The Eastern Cooperative Oncology Group (ECOG) trial 1684 [10] was the first to show some benefit in melanoma. While the initial reports showed a favorable response in a minority of patients, subsequent studies have not clearly confirmed these results [12]. Trials have been conducted with both high dose interferon and low dose interferon in the adjuvant setting.