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The use of interferon in melanoma patients: A systematic review

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ABSTRACT

Interferon (IFN) and PEG-IFN are the only drugs approved as adjuvant therapy in patients with melanoma at high-risk of recurrence after surgical resection. Several clinical trials of adjuvant IFN, using different doses and durations of therapy, have been conducted in these patients. Results generally suggest relapse-free survival and overall survival benefits; however, questions over the optimal dose and duration of treatment and concerns over toxicity have limited its use. IFN exerts its biological activity in melanoma via multiple mechanisms of action, most of which can be considered as indirect immunomodulatory effects. As such, IFN may also be of benefit in the neoadjuvant setting, where it may have a role in melanoma patients with locally advanced disease for whom immediate surgical excision is not possible. However, this has not been well studied. The use of IFN in patients with metastatic melanoma is controversial, with limited data and no convincing evidence of a survival benefit. However, IFN therapy combined with novel biological and immunotherapies offers the potential for a synergistic effect and improved clinical outcomes. Predictive and prognostic factors to better select melanoma patients for IFN treatment have been identified (e.g. disease stage, ulceration, various cytokines) and may also enhance its therapeutic efficacy, but their incorporation into the clinical decision-making process requires validation in prospective trials. In conclusion, the modest efficacy of IFN shown in clinical trials is largely a reflection of differences in response between patients. Despite advancements in the understanding of its biological mechanisms of action, the huge potential of IFN remains to be fully explored and utilized in patients with melanoma.

1. Introduction

The incidence of cutaneous melanoma has been steadily climbing in Western countries, mainly because of increased skin exposure to ultraviolet radiation as a result of changes in travel, leisure activities and fashion. Although prevention campaigns have increased awareness of the risk of melanoma and have contributed to a trend toward thinner melanomas, incidence of melanoma in the US rose from 22.8 to 28.9 cases per 100 000 among white persons between 2000 and 2009. Interestingly, data show increasing melanoma rates of 3.6% per year among women aged 15–39 years compared with 2% per year among men in the same age group [1]. Similarly, incidence rates in Europe are expected to rise to 40–50/100 000 inhabitants/year [2].

While melanoma can be cured by surgical excision if diagnosed in its early stages, metastatic disease is usually refractory to conventional cytotoxic agents and is often rapidly fatal [3], although novel immunotherapies such as ipilimumab and targeted agents such as the BRAF and MEK inhibitors have recently improved prognosis [4,5]. Moreover, patients with regional lymph-node involvement carry a substantial risk of recurrence despite lymph-node dissection, with 5-year overall survival rates ranging from 53% for one positive node to 25% for >4 positive nodes, as reported in a series involving 2505 patients [6]. Sentinel-node biopsy provides valuable staging and prognostic information of intermediate-thickness or thick primary melanomas, with prolongation of disease-free survival (DFS) for all patients and melanoma-specific survival for patients with nodal metastases [7]. In patients with lymph-node involvement and in selected patients with high-risk, node-negative disease, interferon (IFN)-α is the only treatment which is able to prolong DFS, and, to a lesser

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extent, overall survival (OS) [8]. Evidence from a large number of prospective randomized trials is reviewed here along with multiple meta-analyses on the adjuvant use of IFN. Understanding the biological mechanisms and identifying predictive factors for IFN efficacy are mandatory to optimize the use of this powerful treatment, and are also discussed in this review.

1.1. Evidence acquisition

A systematic analysis of the literature was conducted for the period from January 1st, 1990 to October 1st, 2014, by performing a Mesh search on PUBMED using the words 'interferon', combined with the Mesh term 'melanoma'. English language articles that reported treatment and toxicity data from phase II to IV trials were considered for inclusion. A separate search was conducted on PUBMED to identify meta-analyses using the term 'meta-analysis'. No temporal limit was applied to this search. Abstracts published by the American Society of Clinical Oncology and the European Society of Medical Oncology between 2005 and 2014 were also considered, but priority for inclusion was given to peer-reviewed full articles.

2. Mechanisms of action

IFN exerts its biological activity in melanoma via multiple mechanisms of action, most of which can be considered as indirect immunomodulatory effects. These include an increase in tumor-infiltrating cells, decrease in circulating T-regulatory cells (Tregs), manifestations of autoimmunity and development of autoantibodies, changes in cytokine concentrations, modulation of STAT1/STAT3 balance in tumor cells and host lymphocytes, and normalization of T-cell STAT 1 signaling defects in peripheral blood lymphocytes [9].

One study in melanoma patients treated with neoadjuvant therapy found that IFN decreased pSTAT3 and total STAT3 levels on immunohistochemistry (IHC) in tumor cells and lymphocytes, providing in vivo evidence of an indirect immunomodulatory mechanism [10,11]. In the same study, phospho-ERK1/2 and EGFR levels in tumor cells were also down-regulated by neoadjuvant high-dose IFN, although the clinical significance of such effects is not known [12]. In a study of 179 patients with high-risk melanoma and 378 healthy controls, treatment with IFN alfa-2b therapy significantly increased levels of antiangiogenic IFN-γ inducible protein 10 (IP-10) and IFN-α. Pretreatment levels of the proinflammatory cytokines interleukin (IL)-1β, IL-1α, IL-6, TNF-α, and the chemokines macrophage inflammatory protein (MIP)-1α and MIP-1β were found to be significantly higher in the serum of patients with relapse-free survival (RFS) of 1–5 and >5 years when compared with patients with RFS of <1 year. Interestingly, this panel of soluble factors distinguished 96.5% of melanoma patients from healthy controls [13].

Both $CD8^+$ and $CD4^+$ tumor-reactive tumor infiltrating lymphocytes are able to mediate a significant immune response in melanoma patients [14]. One study conducted in patients with stage IIIB melanoma treated with high-dose IFN-α 2b found a significant increase in the number of antigen-presenting cells infiltrating the tumor, along with an increase in peritumoral $CD4^+$ cell infiltrate after 4 weeks of treatment [15]. In another study in 200 patients, IFN therapy induced autoantibodies and clinical manifestations of autoimmunity in 26% of patients. In univariate and multivariate regression analyses, autoimmunity was an independent prognostic marker for improved RFS and OS [16].

IFN-α is able to activate the STAT pathway in lymphocytes via phosphorylation of STAT1. One study assessing pure sorted lymphocytes of peripheral blood found that STAT1 was phosphorylated in response to in vitro exposure to IFN-α in a significantly lower percentage of lymphocytes in melanoma patients ($n = 12$) compared with healthy individuals ($n = 12$). Melanoma patients could be divided into responders (33%) and non-responders (67%), which may help to explain the heterogeneous therapeutic efficacy of IFN in melanoma [17].

Tregs are lymphocytes that can suppress the generation of memory T-cells, with inhibition of primary responses to tumor/self-antigens in tumor-bearing hosts [18]. Ascierto et al. evaluated Treg levels in 22 melanoma patients undergoing adjuvant therapy and in 20 healthy individuals [19]. Subgroup analyses showed that higher baseline Treg levels were associated with more advanced disease stage, earlier recurrence and worse prognosis. The non-statistically significant trend for the reduction in Treg levels observed following IFN-α 2b treatment (average decrease of 0.29% per week) might be related to the limited sample size of the study, rather than to the lack of biological activity of IFN on Treg cells and suggests the need for further studies to verify such associations.

The in vivo and in vitro effects described here provide the biological rationale for IFN activity, and might serve as early markers of IFN efficacy in melanoma patients, as well as potential targets for additional therapeutic options in both the adjuvant and metastatic setting.

3. Interferon in melanoma

3.1. Trials in the adjuvant setting

In melanoma patients with a high-risk of recurrence after surgical resection (stage II B-C and stage III according to the American Joint Committee on Cancer), rates of disease recurrence range between 20 and 60%, with 5-year OS varying between 45 and 70% [20]. IFN-α is the only drug approved by the US Food and Drug Administration (FDA) as adjuvant therapy in these patients, with approval in 1996 based on the results of the ECOG 1684 trial in which it was shown that high-dose IFN-α (HD-IFN) improved RFS and OS [21]. In this study, HD-IFN treatment included an induction phase (20 MU/m^2 intravenously [IV] for 5 days per week for 4 weeks) followed by maintenance stage therapy (10 MU/m^2/day subcutaneously [SC] for 48 weeks). Adverse effects included fatigue, myalgia, depression, increase of alanine and aspartate aminotransferases and pyrexia. Two subsequent trials (ECOG 1690 and ECOG 1694) demonstrated a significant treatment benefit of HD-IFN versus low-dose (LD)-IFN and of HD-IFN versus GM2-KLH/QS-21 vaccine in terms of RFS, but not in terms of OS in melanoma patients at high-risk of recurrence [22,23]. IFN was subsequently approved by the European Medicines Agency (EMA) in 2004. Several clinical trials of adjuvant IFN, using different doses and duration of therapy, have been conducted in high-risk melanoma patients and are summarized in Table 1.

The Hellenic Cooperative Oncology Group conducted a multicenter randomized trial of 1 month versus 1 year with HD-IFN-α 2b in stage IIB/III melanoma patients. IV induction with 15 MU/m^2/day was well tolerated and reduced the risk of relapse [24]. The median RFS was 24.1 months versus 27.9 months ($p = 0.9$) and the median OS was 64.4 months versus 65.3 months ($p = 0.49$) for the 1 month and the full year treatment respectively.

In a randomized phase III Italian Melanoma Inter-group trial in stage III melanoma, patients received a shorter course of IFN-α 2b at higher doses than the ECOG 1684 regimen (20 MU/m^2 IV for 5 days per week for 4 weeks, repeated for three times on weeks 9–12, 17–20, and 25–28 or 20 MU/m^2 IV for 5 days per week for 4 weeks followed by 10 MU/m^2 SC three times per week for 48 weeks). Four cycles of intravenous HD-IFN-α 2b appeared to be well tolerated. The same group reported that shorter but more intensive HD-IFN therapy is feasible and no more toxic than longer courses of HD-IFN, with no differences in efficacy being observed [25].