EUROPEAN JOURNAL OF CANCER 46 (2010) 41–46

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Review

Pegylated interferons: Prospects for the use in the adjuvant and palliative therapy of metastatic melanoma

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ARTICLE INFO

Article history:
Received 15 July 2009
Received in revised form 23 September 2009
Available online 24 October 2009

Keywords:
Malignant melanoma
Pegylated interferon
Adjuvant treatment
Immunotherapy
Conventional interferon

ABSTRACT

Classic interferon-α formulations have antitumour activity in a variety of neoplastic diseases, including the adjuvant and palliative setting of metastatic melanoma, as single agents or in combination with chemotherapy and/or interleukin-2. Pegylated interferon, widely used for the treatment of hepatitis, seems to be at least equally efficacious as standard recombinant interferon in the treatment of metastatic melanoma, and the available evidence suggests that equi-efficacious doses have somewhat lower acute toxicity. Moreover, the favourable pharmacokinetic properties of pegylated interferon allow the administration on a weekly basis, with sustained exposure to interferon during that entire period.

Several clinical trials have been conducted testing adjuvant and palliative treatment with pegylated interferon-α in high-risk melanoma patients with promising results. The role of pegylated interferons in the setting of advanced metastatic melanoma will need further investigation in clinical trials, potentially in combination with targeted or cytotoxic agents with regard to synergistic antiangiogenic and cytotoxic effects. The use of pegylated interferons in earlier stage melanomas will be investigated in upcoming trials.

1. Introduction

Since the 1980s, the interferons have played an important role in the treatment of high-risk primary and metastatic melanoma. Two subtypes have been developed for therapeutic purposes so far, interferon-α2a (Roferon-A®, Roche Pharmaceuticals, Basel, Switzerland) and interferon-α2b (Intron-A®, Schering Plough, Kenilworth, NJ, USA). These two interferons differ from each other in only two of the 166 amino acids, and they are nearly identical in their therapeutic effects and in their toxicity profiles. Interferon-α belongs to the class of type I interferons and binds to the interferon type 1 receptor. The signalling cascade which is mediated by the receptor binding of interferon-α is rather well understood[1] (Fig. 1). Binding of interferon-α to the receptor activates two Janus kinases: tyk-2 and JAK-1. Activated Janus kinases recruit stat factors in the cytoplasm. Six different stat factors are presently known. Two stat factors form dimers, which are capable of transport to the nucleus. In combination with the additional stabilising molecules, they form interferon-stimulated gene factors in

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.10.004

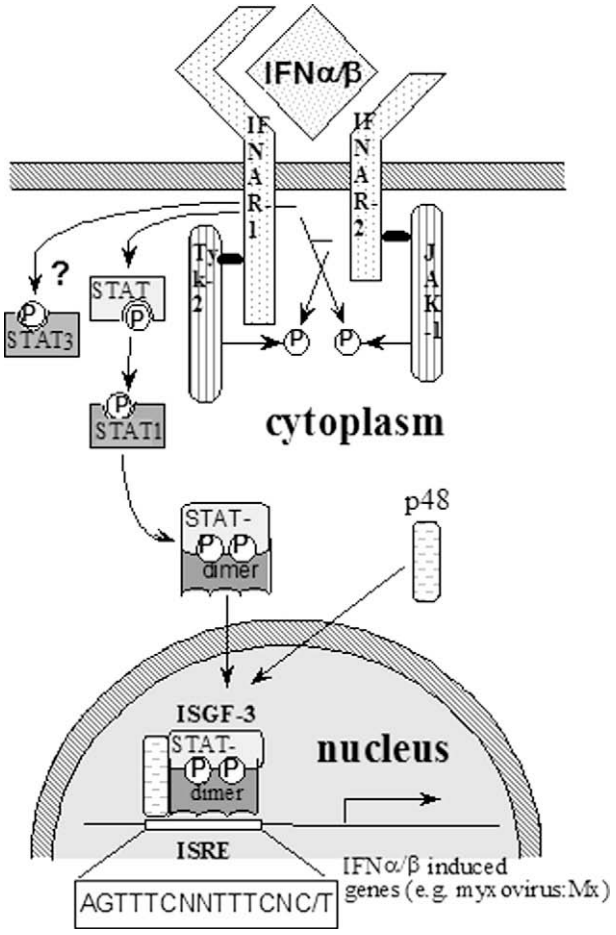

Fig. 1 – IFN signal transduction. The binding of IFN proteins to their specific receptor rapidly induces tyrosine phosphorylation of the receptor by JAK kinases; these phosphorylated tyrosines provide a docking site for the STAT proteins which are subsequently phosphorylated by the Jak kinases. Activated STAT proteins dimerise to one another. Dimeric STAT then translocates into the nucleus and acts by direct binding to DNA. In combination with additional stabilising molecules, they form interferon-stimulated gene factors in the nucleus. These bind to interferon-stimulated response elements at the DNA which are a specific DNA sequence comprising 14 base pairs.

the nucleus. These bind to interferon-stimulated response elements at the DNA level, which are specific DNA sequences comprising 14 base pairs. There they act as transcription factors and activate a number of genes. Among these are genes responsible for virus inhibition such as the MX proteins (myxovirus proteins, inhibiting viral replication), 2́5́-OAS (2′-5′-oligoadenylate synthetase, induces mRNA degradation) and PKR (RNA-dependent protein kinase, inhibiting translation). Additional genes are involved in immune regulation such as the activation of IL-12, IL-15 and interferon-γ. Likewise, up-regulation and expression of toll-like receptors are induced by interferon-α. A third major effect of interferon-α is growth inhibition of tumour cells, which is mediated by the activation of p21 and the p200 family, which mediate growth arrest. Furthermore, caspases are activated, which mediate cell death. Interferon-α has also been shown to be important for differentiation and maturation of dendritic cells.[2] Thus, the three main effects of interferons-α are the inhibition of viral growth, growth inhibition of tumour cells and immuno-stimulatory effects by activation of different cytokines.

2. Differences of pegylated interferon-α compared to classic interferon-α

Interferon-α subtypes as produced by recombinant DNA technology are pure proteins without any side chains. Natural interferon-α proteins, however, are glycosylated. This influences the pharmacokinetics of these molecules. Pegylation refers to the addition of polyethylene glycol (PEG) to proteins; either one or several side chains of PEG bind to the protein molecule. This chemical modification influences the pharmacokinetics and the half-life time of the molecule (Table 1). The half-life in the serum is clearly prolonged for pegylated interferon-α at 40–60 h compared to 3–6 h for classic interferon-α.[3] Furthermore, the route of excretion is changed from renal elimination to hepatic elimination. The clearly longer half-life of pegylated interferon-α allows once weekly application instead of the three times weekly application of classic interferon-α. Currently, two types of pegylated interferon products are in use and under investigation for malignant melanoma: pegylated interferon-α2a (Pegasys®, Roche) and pegylated interferon-α2b (PEG-Intron®, Schering-Plough). Additionally, the efficacy of pegylated interferon-α seems to be increased, at least in its antiviral activity. Elimination rates of the viral load in hepatitis B and C are clearly more effective with the use of pegylated interferon-α as compared to classic interferon-α.[4–6] Therefore, there is some hope that pegylated interferon-α may likewise be more effective in the treatment of malignancies. There are some hints from renal cell cancer and from chronic lymphatic leukaemia that pegylated interferon-α is an effective agent for treating cancer.[7] It is an important question whether the action of pegylated interferon-α parallels that of classic interferon. This question had been addressed in a SCID mouse model carrying tumours of a melanoma cell line.[8] It has been shown that pegylated interferon-α2a has very similar growth inhibitory effects to classic interferon-α in this xenogenic tumour model. Furthermore, the pattern of gene activation and gene silencing was nearly identical for both pegylated and classic interferon-α. Therefore, the mode of action of both interferons seems to be similar if not identical, and differences in their efficacy seem to be attributed to the different pharmacokinetics.

3. Adjuvant treatment with interferon-α

Classic interferon-α has shown over the last two decades to have some beneficial effects in the adjuvant treatment of high-risk cutaneous melanoma patients. Since no other drug so far has shown comparable clinical effects, classic interferon-α is well established in the adjuvant treatment in clinical stages II and III, although a survival benefit for melanoma patients treated with interferon-α has not convincingly been demonstrated. In Europe, low-dose interferon is approved

Table 1 – Pharmacokinetics of conventional interferon-α2a and of pegylated interferon-α2a and 2b.

	IFN-α2a	PEGIFN-α2b	PEGIFN-α2a
Half-life	3–8 h	27–39 h	50–130 h
Time to serum peak	7–12 h	15–44 h	27–96 h
PEG chain	–	12 kD linear	40 kD arborised
Clearing	Renal	Renal	Hepatic

and widely used for stage II melanoma patients. In contrast, in the United States (US) only high-dose interferon is approved for stage III melanoma patients. Two different treatment regimens have been in widespread use, characterised as using high or low dosages of interferon-α. Significant benefits in terms of recurrence-free and overall survival have been shown for both regimens in individual trials.[9–13] However, other studies were unable to replicate all those beneficial effects.[14–18] A recent meta-analysis of all available interferon data in melanoma, involving more than 6000 patients, detected a highly significant impact on relapse-free survival.[18]

In addition, a small but statistically significant improvement in overall survival in the range of 3% for the entire study population was detectable.[19] Dosage and duration of treatment could not be clearly established to have a significant impact on the clinical benefits of therapy when the results of all available interferon clinical trials have been analysed.[18–22]

4. Adjuvant treatment with pegylated interferon-α

Several clinical trials have been conducted testing adjuvant treatment with pegylated interferon-α in high-risk melanoma patients (Table 2). One large trial performed by the European Organisation for Research and Treatment of Cancer (EORTC), EORTC 18991, was first reported in 2007. This trial recruited 1256 patients with microscopic or macroscopic lymph node metastasis between July 2000 and August 2003.[23] Patients were randomised after complete resection of the primary tumour and/or the regional nodes either to treatment with pegylated interferon-α2b (PEG-Intron®) 6.0 μg/kg per week for the first 8 weeks followed by a long-term maintenance treatment period of 5 years with 3.0 μg/kg per week or to observation without adjuvant therapy. The study was initially designed to detect an improvement in distant metastasis-free survival for pegylated interferon treatment. Because of the pivotal character of this clinical trial, the US Food and Drug Administration (FDA) requested a change of the primary study end-point from distant metastasis-free survival to relapse-free survival before any statistical evaluations were done.

The distribution of patients in both arms was highly comparable. For patients randomised to pegylated interferon, the 8-week induction phase was completed in almost all patients. However, maintenance treatment lasted only for a median duration of 12 months. The main reason for treatment discontinuation in almost half of the patients was disease progression. In one-third of the patients, toxicity issues led to treatment discontinuation. Thus, only 22.5% of melanoma patients remained on treatment with pegylated interferon-α2b at year 5. The main toxicities (Common Terminology Criteria for Adverse Events [CTCAE] grade 3/4) were liver toxicity (11%), fatigue (16%) and depression (6%).

The 4-year rate of recurrence-free survival was 45.6% in the interferon group and 38.9% in the observation group. Relapse-free survival time was significantly prolonged from 25.5 months in the observation arm to 34.8 months in the pegylated interferon-α2b arm ($p = 0.011$). The overall survival curves in the ITT analysis were overlapping in both groups for the entire study population. Additional analyses were performed taking into account tumour load (N1, microscopic tumour invasion versus N2, macroscopic involvement), as well as ulceration of the primary tumour.[23]

The effects of treatment with pegylated interferon-α2b were more pronounced in patients with microscopic stage III melanoma disease than in those with bulkier disease.[23] Among patients with microscopic nodal disease (N1), there were fewer recurrences or deaths in the interferon group than in the observation group. Likewise, there were fewer distant metastases or deaths in the interferon group than in the observation group.[23] Kaplan–Meier curves for patients with microscopic nodal disease (N1) showed that the effect of pegylated interferon began quite early in the study and was maintained throughout the follow-up period. By contrast, among patients with palpable nodal disease (N2), similar numbers of recurrences, distant metastases and deaths were seen in the two groups.[23] It should be noted that lower rates of recurrence, distant metastasis and death were also seen in patients with tumour involvement limited to one lymph node, regardless of whether it was microscopic or macroscopic, who were randomly allocated to received interferon

Table 2 – Overview on adjuvant trials with pegylated interferon.

	Stage	Drug	Protocol
Garbe (DeCOG)	IIA (T3)- IIIB	IFN-α2a (Roferon®) versus PEGIFN-α2a (Pegasys®)	3 × 3 Mio IE IFN-α2a weekly versus 180 μg PEGIFN-α2a weekly, treatment duration 24 months
Garbe (EADO)	IIA-IIIB	IFN-α2b (Intron®) versus PEGIFN-α2b (PEG-Intron®)	3 × 3 Mio IE IFN-α2b weekly for 18 months versus 180 μg PEGIFN-α2a weekly for 36 months
Eggermont (EORTC)	IIIA-IIIC	PEGIFN-α2b (PEG-Intron®) versus observation	6 μg PEGIFN-α2a weekly for 8 weeks (induction) 3 μg PEGIFN-α2a weekly for 60 months (maintenance)

than in those in the observation arm.[23] In the subgroup of patients with microscopic involvement of any number of nodes and who had ulceration in the primary tumour ($n = 186$), pegylated interferon-α2b seemed to reduce the risk of recurrence, distant metastasis and death.[23]

Hence, ulceration of the primary melanoma seemed to indicate a particular sensitivity to the benefits of an interferon treatment. Whether this observation holds true will be tested in a subsequent EORTC trial 18081 in melanoma patients which ulcerated primaries and a tumour thickness of more than 1 mm which will be initiated in early 2010. A recent update on this trial revealed, not surprisingly, that quality of life is negatively affected – albeit to only a modest degree – by treatment with pegylated interferon-α2b. Differences were found for social and role functioning, appetite, weight loss and dyspnoea.[24]

Another trial has been initiated by the European Association of Dermatologic Oncology (EADO) lead by C. Garbe (Germany), H. Pehamberger (Austria) and M. Delaunay (France). In this trial, patients with stages II and III melanoma have been recruited. This comprises patients with more than 1.5 mm tumour thickness, including a subset of around 10% who have been found positive for micrometastatic disease by sentinel lymph node biopsy. The trial recruited 890 patients who were randomised into the following arms: pegylated interferon-α2b 100 μg once weekly for 36 months versus treatment with low-dose interferon-α2b 3 MIU thrice weekly for 18 months, which is an approved dosing regimen in Europe. Recruitment goals were reached in June 2005. The study is powered to detect a 10% improvement of disease-free survival at 5 years as the primary study end-point.

A third trial led by C. Garbe has been initiated by the German Dermatologic Cooperative Oncology Group (DeCOG) in which pegylated interferon-α2a (Pegasys®) is being tested. The trial has recruited 880 melanoma patients in stages IIA and IIIB (Table 2) between October 2004 and May 2007. The patients were randomised into two arms: Treatment with 180 μg pegylated interferon-α2a (Pegasys®) weekly for 24 months versus treatment with classic interferon-α2a (Roferon-A®) 3 MIU thrice weekly for 24 months. The study was powered to detect a 10% improvement of distant metastasis-free survival at 5 years. Although both studies have completed patient enrolment, no data are available about the results of either study at this time.

5. Stage IV melanoma treatment with conventional and pegylated interferon-α

Patients with malignant melanoma and distant metastasis generally have an unfavourable prognosis. Mean survival of patients after the diagnosis of stage IV disease is 6–12 months and about 20% of patients survive 1 year.[25] Many attempts have been made over the past few decades to influence the course of the disease by systemic therapy. In multi-institutional studies, only 6–15% of the patients show a transient response to single agent chemotherapy.

Some hope was initially raised by the use of recombinant cytokines and in particular of interferons. An analysis of studies performed in the 1980s and early 1990s involving over 500 patients revealed response rates of 11–14% for recombinant interferon-α2a and α2b.[26] These results indicate that the effectiveness of interferon-α is in a range comparable to single agent chemotherapy in stage IV melanoma. Like single-agent chemotherapy, responses to interferon were most common in patients with soft tissue and lung metastases, and less common in patients with visceral disease.

A phase I/II study on pegylated IFN-α2b in patients with solid tumours also included six melanoma patients.[17] The patients received 0.75–7.5 μg/kg/week of pegylated IFN-α2b by subcutaneous injection for 12 weeks. Patients with a response or stable disease after 12 weeks were eligible for the extension protocol and were treated for up to 1 year or until disease progression. Two melanoma patients showed long-lasting complete response (267+ days, 291+ days). This study confirmed that pegylated IFN-α2b is safe and well tolerated in patients with advanced solid tumours.[7] So far, only one open label, randomised multicentre phase II study has been conducted in metastatic melanoma in order to assess the efficacy of pegylated interferon-α.[27]. The patients received one of the three subcutaneous doses of pegylated interferon-α2a (Pegasys®) consisting of 180 μg ($N = 48$), 360 μg ($N = 53$) and 450 μg ($N = 49$). The drug was administered weekly for 24 weeks or until disease progression. A dose-dependent objective response rate (complete plus partial responses) of 6% in the 180 μg arm, 8% in the 360 μg arm and 12% in the 450 μg arm has been observed.[27]

A DeCOG (Dermatologic Cooperative Group) phase II trial investigated the efficacy of pegylated interferon-α2b (100 μg weekly) in combination with temozolomide (200 mg/m^2 days 1–5, every 28 days).[28] In all, 116 of 124 patients were assessable for response: 2 melanoma patients (1.7%) had a complete response and 19 (16.4%) achieved a partial response (overall response rate: 18.1%). A total of 25.0% had disease stabilisation while 56.9% progressed during therapy. Overall survival was 9.4 months; progression-free survival was 2.8 months. In 20.7% of the patients CTCAE grade 3/4 thrombocytopaenia occurred, while 23.3% had grade 3/4 leucopaenia. These results, both in terms of response rates and toxicity, are at least comparable to published data of the combination of temozolomide with non-pegylated IFN, and perhaps better than those expected for temozolomide as a single agent.

The combination of dacarbazine (850 mg/m^2 every 3 weeks) and pegylated interferon-α2a (weekly 180 μg) as a first-line therapy has been investigated in a phase II trial.[29] A complete response occurred in two patients (8%), lasting for more than 1 and 2 years, respectively.[28] A partial remission was reached in four patients (16%), and one patient had stable disease. The median duration of responses was 8 months, the median progression-free survival was 2 months. The median overall survival time was 13 months. The safety profile revealed mainly affected haematologic side-effects with relatively few grade 3 toxicities and only one grade 4 toxicity.

Prior adjuvant interferon seemed to affect the outcome of therapy with dacarbazine and pegylated interferon in this trial. Of the 6 patients with clinical responses and the 1 patient with a stable disease as the best response, only 2 patients had received prior interferon and only 1 of these demonstrated disease progression during adjuvant interferon treatment.

Six of the 7 patients who developed disease tumour progression during adjuvant interferon treatment also developed progressive disease on this trial.[29] Overall, the combination of pegylated interferon and either dacarbazine or temozolomide was found to be well tolerated, and efficacy was sufficiently encouraging to warrant evaluation in larger trials.

Pegylated interferon is also being combined with other investigational agents in metastatic melanoma. Currently a phase II DeCOG trial investigates the efficacy of the multikinase inhibitor sorafenib (400 mg bid) in combination with pegylated interferon-α2b (37 μg per kg weekly) for a maximum of 48 weeks or until disease progression as first-line treatment in 55 melanoma patients. Previous clinical trials in renal cancer cell patients who have been treated with a combination regimen of conventional interferon and sorafenib demonstrated clinical efficacy with a safety profile which seems to overlap partially, for example, thrombocytopaenia or fatigue.[30,31] The role of pegylated interferons in the setting of advanced metastatic melanoma will need further investigation in clinical trials, mostly in combination with targeted or cytotoxic agents to provide potential synergistic effects.

6. Conclusion

The use of pegylated interferons in the adjuvant and palliative setting of metastatic melanoma still needs further investigation in clinical trials. However, to date pegylated interferons have not been established as a new standard of care. Compared to high-dose interferon-α2b pegylated interferons demonstrate a more favourable tolerability and may be used as an alternative.

Conflict of interest statement

Kaehler: travel grant Essex Pharma; Sondak: consultant and speakers bureau Schering-Plough; Schadendorf: grant/research/honorarium Schering-Plough; Hauschild: consultant and speakers bureau Schering-Plough.

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