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Utility of adjuvant systemic therapy in melanoma

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The lack of effective drugs in stage IV melanoma has impacted the effectiveness of adjuvant therapies in stage II/III disease. To date, chemotherapy, immunostimulants and vaccines have been used with minimal success. Interferon (IFN) has shown an effect on relapse-free survival (RFS) in several clinical trials; however, without a clinically significant effect on overall survival (OS). A recently conducted meta-analysis demonstrated prolongation of disease-free survival (DFS) in 7% and OS benefit in 3% of IFN-treated patients when compared with observation-only patients. There were no clear differences for the dose and duration of treatment observed. Observation is still an appropriate control arm in adjuvant clinical trials. Regional differences exist in Europe in the adjuvant use of IFN. In Northwest Europe, IFN is infrequently prescribed. In Central and Mediterranean Europe, dermatologists commonly prescribe low-dose IFN therapy for AJCC stage II and III disease. High-dose IFN regimens are not commonly used. The population of patients that may benefit from IFN needs to be further characterised, potentially by finding biomarkers that can predict response. Such studies are ongoing.

Key words: adjuvant therapy, interferon, melanoma, metastasis, randomised trials

systemic adjuvant therapies (chemotherapy, non-specific immune stimulants and vaccines)

No less than 25 randomised trials have been conducted in stage II/III melanoma in order to evaluate adjuvant therapies, such as chemotherapy, non-specific immune stimulants such as bacillus Calmette-Guerin (BCG), *Corynebacterium parvum*, levamisole or combinations of these agents with dacarbazine chemotherapy. These trials were almost invariably underpowered and yielded negative results with the exception of occasional, incidental and non-repeatable positive findings in trials involving small numbers of patients [1].

Of seven large, randomised trials of allogeneic melanoma cell-based vaccines conducted, only one trial came close to demonstrating a treatment benefit. This was an Australian study investigating an allogeneic tumour cell-based oncolysate [2]. In the United States, a trial of the Melacine vaccine in stage II patients showed no benefit for the total study population [3], but there appeared to be some activity in patients with particular HLA types [4]. Unfortunately, a prospective study of the vaccine in patients with these HLA types has not been conducted. In 2006, there were negative results reported from two large, randomised trials of Canvaxin, an allogeneic tumour cell-based vaccine, in patients with stage III and resected stage IV disease. Patients in the vaccine arms of these trials had worse outcomes than those in the control arms [5]. Canvaxin had shown great promise in early case–control studies. The result of these two trials is a powerful reminder of the unreliability of such methodology. It demonstrates the limited value of such data, which should be restricted to generating hypotheses [6].

There was a small, phase III trial of the ganglioside GM2 that demonstrated a survival benefit for stage III patients. However, this benefit was observed in only a subset of patients who were sero-negative for ganglioside antibodies before trial entry [7]. This study led to the European Organisation for Research and Treatment of Cancer (EORTC) conducting a phase III adjuvant trial of GM2 in patients with stage II disease (18961) where 1314 patients were accrued and ~50% of these patients were staged by sentinel node biopsy. At the second interim analysis (2007), it appeared that there might be a detrimental outcome for survival in the vaccine arm, which led to an early termination of this trial [8]. The final outcome is not yet known.

interferon alpha

clinical trial data

The use of high-dose IFN (HDI, 20 MIU/m^2 i.v. 5 days per week for 4 weeks, 10 MIU/m^2 s.c. 3 days a week for 48 weeks)

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therapy is approved by both the FDA in the United States and EMEA in Europe for patients with high-risk melanoma (stage IIB/III). HDI is commonly used in the United States, although it is not commonly used in Europe. The therapeutic impact on OS is uncertain and considered modest at best, the side-effect profile is significant and the cost can be relatively high [1, 9].

Gogas et al. [10] recently reported that 4 weeks of intravenous IFN (15 MIU i.v. 5 days per week for 4 weeks) was as good as the 4-week regimen followed by 10 MIU flat dose s.c. 3 days a week for 48 weeks), and was much better tolerated. The dosing schedule used in that trial differs from the HDI regimen approved by the FDA and EMEA.

The ECOG is currently conducting an adjuvant trial in patients with stage II (T3N0, tumour thickness 1.5–4.0 mm) or stage III (T4N0, tumour thickness >4 mm) melanoma without nodal involvement and in patients with stage III (T1–4, N1) melanoma with a microscopically positive lymph node (ECOG 1697), comparing 4 weeks of high-dose IFN-α2b with observation alone. Due to the present rates of accrual, it is likely that these results will not be available before 2010.

Intermediate doses of IFN (IDI) were tested in patients with stage IIB/III disease in the largest phase III trial to date (EORTC 18952). The results demonstrated a statistically insignificant 7.2% increase in distant metastasis-free interval (hazard ratio 0.83; 97.5% CI 0.66–1.03; $P = 0.05$) and a 5.4% increase in OS (hazard ratio 0.85; 97.5% CI 0.68–1.07; $P = 0.12$) at 4.65 years of follow-up.

The increase in OS was observed only in patients treated for 25 months with 5 MIU IFN-α2b and not in those treated for 13 months with 10 MIU IFN-α2b [11].These results suggested that duration of therapy might be more important than dose.

The question of treatment duration was addressed in the next EORTC trial (18991) in which patients were randomised to 5 years of pegylated IFN-α2b (PEG-IFN) or to observation alone [12]. In this trial, the dosing schedule was comparable to that of HDI. PEG-IFN was administered for an induction period of 8 weeks at 6 μg/kg body weight, followed by long-term maintenance dosing of 3 μg/kg for the remaining 5 years. This was a registration study, and the trial endpoint set by the regulatory authority was relapse-free survival (RFS), although the primary endpoint of the trial was distant metastasis-free survival (DMFS) with OS and toxicity as secondary endpoints.

The trial results to date are consistent with that of other phase III trials of adjuvant IFN having a significant effect on RFS and no significant impact on DMFS or OS at 4 years (Table 1). In patients with only microscopic involvement of regional lymph nodes (sentinel node biopsy-positive patients, N1) the impact on DMFS was statistically significant (Table 2), with a trend to prolongation of OS, compared with those patients with palpable disease. In those with palpable nodal involvement (N2), there was no significant impact of PEG-IFN therapy on either endpoint. The benefits in OS and DMFS for patients with microscopic nodal involvement were very similar to those observed in the 25-month IFN treatment arm in the EORTC 18952 trial.

Table 1. Significant impact of pegylated IFN-α2b (PEG-IFN) on disease-free survival (DFS) but not on distant metastasis-free survival (DMFS) and overall survival (OS) in patients with stage III melanoma (data taken from ref. [12])

	DFS	DMFS	OS
PEG-IFN[a]	45.6% (2.2)	48.2% (2.2)	56.8% (2.2)
Observation[a]	38.9% (2.2)	45.4% (2.3)	55.7% (2.1)
HR (95% CI)[b]	0.82 (0.71–0.96)	0.88 (0.75–1.03)	0.98 (0.82–1.16)
P-value[b]	0.01	0.11	0.78

[a]4-year rate (SE).
[b]Univariate analysis.

Thus, a significant or borderline significant impact on early stage III disease has been observed in two consecutive EORTC trials involving 2644 patients, whereas there was no impact on outcome in patients with palpable nodal involvement in either study. This observation underscores the value of sentinel node (SN) biopsy as the current widespread practice that enables accurate patient staging at trial entry. A Dermatological Cooperative Oncology Group (DeCOG) study compared administration of low-dose IFN-α2a (3 × 3 MIU/week) for 18 months, as approved in Europe, with administration for 60 months. The trial included 850 patients with primary melanoma of >1.5 mm tumour thickness, with the majority of the patients staged by sentinel node biopsy. No difference in disease-free survival (DFS) or OS has been observed between the groups so far [13].

Low-dose IFN trials. The effect of low-dose IFN (LDI) in stage II and III melanoma was also tested [14]. In stage II, LDI had a consistent and significant effect on DFS in the French [15], Austrian [16] and Scottish [17] studies, with even a borderline significant effect on OS in the French trial [15] (Table 3). LDI regimens of 2 and 3 years in stage IIB and III disease were tested in the Intergroup 1690 [18] and in the UKCCR Aim High [19] trials with a similar small effect on DFS. The WHO-16 trial, which evaluated 3 years of LDI in stage IIIB or IIIC patients, was negative for both DFS and OS [20]. Thus, earlier disease appears more responsive to LDI than more advanced disease.

In contrast, very recent results of a LDI DeCOG trial showed improvement in both DFS and OS for low-dose IFN-treated patients compared with untreated controls in stage III melanoma, while the combination of LDI and dacarbazine did not demonstrate any benefit [21]. Low-dose IFN therapy has been approved as an adjuvant therapy for stage II patients by the EMEA in Europe. The effect of IFN in stage II/III patient trials, at the time when these patients were not SN-staged, corresponds well with the observations in the EORTC 18952 and 18991 trials, where the greatest effect was observed in patients with positive sentinel nodes.

At least four prospective, cooperative group, randomised multicentre trials have demonstrated that a combination of low-dose IFN-α with other agents does not improve outcome (Table 4). Patients with stage IIIA, B or C melanoma were treated in a DeCOG trial with dacarbazine plus LDI or LDI alone for 2 years, and compared with observation alone. Surprisingly, the combination of dacarbazine plus LDI diminished the treatment effects observed with LDI alone. The possible detrimental effect of dacarbazine in the adjuvant setting requires further consideration [21].

Table 2. Significant impact of pegylated IFN-α2b (PEG-IFN) on disease-free survival (DFS) and distant metastasis-free survival (DMFS) in stage III melanoma patients with N1 microscopic but not N2 macroscopic nodal involvement (data taken from ref. [12])

	DFS		DMFS	
	N1	N2	N1	N2
[a]PEG-IFN	57.7% (3.3)	36.3% (2.8)	60.5% (3.6)	38.7% (2.8)
[a]Observation	45.4% (3.5)	33.9% (2.6)	52.6% (3.5)	39.9% (2.7)
[b]HR (99%CI)	0.73 (0.53–1.02)	0.86 (0.68–1.10)	0.75 (0.52–1.07)	0.94 (0.73–1.21)
[b]*P*-value	0.016	0.12	0.03	0.53

[a]4-year rate (SE).
[b]Univariate analysis.

Table 3. Low-dose IFN trials in stage II/III melanoma

Trial	Stage	Treatment	DFS	OS
French [15]	II	IFN-α2a, 3 × 3 MIU/week for 18 months	5-year; HR = 0.75; *P* = 0.035	5-year; HR = 0.72; *P* = 0.059
Austrian [16]	II	IFN-α2a, 3 × 3 MIU/day for 3 weeks; 3 × 3MIU/week for 12 months	3.4-year; HR = 0.62; *P* = 0.02	3.4-year; HR = 0.83; not significant
Scottish [17]	IIB, III	IFN-α2b, 3 × 3 MIU/week for 6 months	2-year; HR = 0.72; *P* = 0.05	2-year; HR = 0.81; *P* > 0.2
ECOG 1690 [18]	IIB, III	IFN-α2b, 3 × 3 MIU/week for 24 months	5-year; HR = 0.90; *P* = 0.17	5-year; HR = 0.93; *P* = 0.81
UKCCR [19]	IIB, III	IFN-α2a, 3 × 3 MIU/week for 24 months	5-year; HR = 0.91; *P* = 0.3	5-year; HR = 0.94; *P* = 0.6
WHO-16 [20]	III	IFN-α2a, 3 × 3 MIU/week for 36 months	5-year; HR = 0.95; *P* = 0.5	5-year; HR = 0.96; *P* > 0.5
DeCOG [21]	III	IFN-α2a, 3 × 3 MIU/week, for 24 months	4-year; HR = 0.69; *P* = 0.018	4-year; HR = 0.62; *P* = 0.0045

DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

Table 4. Combination trials with low-dose IFN

Trial	Combination	Stage	DFS	OS
Garbe et al. [21]	IFN-α2a + dacarbazine[a,c]	III	4-year; *P* = 0.97	4-year; *P* = 0.75
Mitchell et al. [22]	IFN-α2b + Melacine[b]	III	5-year, *P* = 0.80	5-year; *P* = 0.57
Hauschild et al. [23]	IFN-α2b + IL-2[c]	II	6.6-year; *P* = 0.93	6.6-year; *P* = 0.93
Richtig et al. [24]	IFN-α2a + isotretinoin[a]	II	5-year; *P* = 0.25	5-year; *P* = 0.80

Control arms: [a]low-dose IFN; [b]high-dose IFN; [c]observation.
DFS, disease-free survival; OS, overall survival.

Another randomised trial of 604 stage III melanoma patients combined an allogeneic melanoma lysate vaccine (Melacine) with low-dose IFN-α. This regimen was compared with high-dose IFN-α2b alone. No differences in DFS or OS were observed [22]. A DeCOG trial of LDI combined with low-dose interleukin-2 (IL-2) presented overlapping survival curves for DFS and OS compared with untreated controls [23]. A randomised, double-blinded, placebo-controlled trial from Austria comparing LDI and isotretinoin with IFN-α alone in stage IIA/IIB melanoma patients was stopped for futility [24].

In conclusion, the combination of low-dose IFN-α with various other agents, which might have an additional or synergistic effect, is no better than LDI or observation alone.

A systematic review of all trials [25], a meta-analysis of all trials [26] and a pooled data analysis of all HDI trials [27] demonstrated a consistent DFS improvement but no statistically significant impact on OS. The clinical relevance of improvements in DFS is unclear and is difficult to quantify. An individual patient data-based meta-analysis was reported at the 43rd Annual Meeting of ASCO in 2007 [14], which confirmed the consistently reported, statistically significant benefit on DFS (7%), and for the first time, a small but statistically significant impact (3%) on OS. This effect is partly due to the inclusion of trials ECOG 1694 and ECOG 2696, which had the ganglioside GM2 vaccine as a comparator arm. The validity of inclusion of these trials has been questioned. The EORTC 18961 trial was terminated based on the second interim analysis of a potential detrimental effect of the vaccine. Another important finding from this individual patient data-based meta-analysis is that the effects of IFN were observed across a wide range of doses. The conclusions drawn were that the therapeutic effect of IFN is not dose related, nor related to treatment duration.

predictive factors: auto-antibodies

Gogas et al. [28] have reported that patients treated with adjuvant IFN who developed auto-antibodies against thyroglobulin, antinuclear antibodies or cardiolipin have a significantly better outcome than patients without these signs of autoimmunity. The observation that autoimmunity is

associated with clinical benefits such as higher response rates and longer DFS and OS has been known for many years. This association not only applies to patients treated with immunotherapy, but also to patients administered chemotherapy and sometimes no therapy at all. The identification of markers that might predict a host antitumour immune response is extremely important. These could be used to determine which patients to treat with IFN and for what duration of time.

An evaluation of the presence or emergence of auto-antibodies in patients who participated in EORTC 18952 did not confirm Gogas's observations [29]. Also, a sub-study of the ECOG 2696 trial did not confirm auto-antibodies as a strong independent prognostic factor [30], nor did antibodies have any prognostic value in EORTC 18991 [31].

In contrast, serial determination of serum S100 levels was demonstrated to be a very powerful prognostic factor in an analysis of the EORTC 18952 trial on intermediate doses of IFN in stage IIB/III patients, and its prognostic value was even superior to the number of positive regional lymph nodes [32].

other ongoing and future trials

Novel targeted agents, anti-angiogenics and immune modulators are being actively investigated in stage IV melanoma, while agents such as bevacizumab and anti-CTLA-4 are already in adjuvant studies. An analysis of the adjuvant phase III trial of anti-CTLA-4 antibody ipilimumab (EORTC 18071) starting in 2008, will not be complete before 2011.

A study of pegylated IFN in high-risk, stage II patients with ulcerated melanomas (EORTC 18081) will begin shortly.

conclusions

After decades of research, cytotoxic drugs, immune stimulants and vaccines have had disappointing results in the adjuvant setting. IFN-α is the major drug that has been considered for adjuvant therapy and is used with various schedules in Europe, both in stage II and in stage III patients. High-dose IFN-α2b has been considered the standard of care in North America for patients with an acceptable performance status. IFN has demonstrated a consistent impact on RFS, with a modest impact on OS. Observation is still an appropriate control arm in adjuvant clinical trials. The population of patients who might benefit from IFN and other adjuvant treatments needs to be identified via new technologies of genomics and proteomics or by identifying novel biomarkers, which can predict potential host immune responsiveness.

The European melanoma community is currently extremely active in the conduct of phase III trials in melanoma. It has played a major role in defining the inefficacy of many adjuvant surgical procedures in melanoma, and in identifying the incremental effects of adjuvant IFN in stage II and stage III melanoma patients. It is hoped that future collaborative studies between the United States, Australia and Europe will lead to the identification of new and more active treatment modalities for melanoma.

conflict of interest disclosures

A. M. M. Eggermont has been consultant for Schering-Plough and Bristol-Myers Squibb; H. Gogas has received honoraria from Schering-Plough; A. Hauschild has received honoraria, consultancy fees and study grants from Schering-Plough/Essex Pharma (Germany) and Roche Pharma (Germany); T. Petrella has had advisory roles with Pfizer, Novartis (Chiron) and Schering-Plough.

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