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Current Perspective

The role interferon-alpha in malignant melanoma remains to be defined

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Abstract

Interferon-alpha (IFNα) is a pleiotropic cytokine with various direct and indirect inflammatory response modulating activities. Some of these activities may have direct or indirect antitumour effects. For such a wide range of biological activities, the dose for optimal biological activity may differ greatly from the maximally tolerated dose as different effects are mediated by different concentrations of IFNα. Because of its immunomodulatory effects, it has been extensively studied in melanoma patients. Little antitumour activity has been demonstrated in metastatic stage IV melanoma, with overall response rates of 10–15%, which were not dose-related. Yet, IFNα has been widely studied in the adjuvant setting for stage II and III disease. Many trials have been underpowered, have used very heterogeneously mixed patient populations, a wide variety of doses and treatment schedules, and have suffered from early and unplanned analyses. Mature data are still pending in some 3000 patients of the overall approximately 6000 patients that participated in the adjuvant trials. A meta-analysis has demonstrated a similar impact on relapse-free survival across various dose ranges of IFNα, but *no* significant impact on overall survival (OS). In light of the lack of impact on OS and the considerable to serious dose-dependent toxicity of IFNα, we do not have a clearly dose- and schedule-defined role for IFNα in the adjuvant setting and have no evidence for a benefit of IFNα in stage IV melanoma. For the adjuvant setting, the main question: efficacy of very toxic high dose therapy versus efficacy of non-toxic long-term treatment will be answered by the mature data from the large US-Intergroup high-dose and EORTC intermediate-dose and long-term maintenance therapy trials.

Keywords: Melanoma; Interferon-alpha; Randomised trial

1. Introduction

Interferon-alpha (IFNα) is a cytokine with various modulating effects on the inflammatory response. These pleiotropic effects may depend on the concentrations of IFNα. They include *direct* antiproliferative and pro-differentiative, as well as protein synthesis-inhibiting antitumour effects, as well as *indirect* antitumour functions including activation of host effector effects that may result from the augmented expression of tumour cell surface antigens, rendering the tumour more susceptible to host effector cells in general [1]. More recently, important data about yet another activity, the anti-angiogenic effects of IFNα, have been reported. Fiddler and collaborators have demonstrated that IFNα-mediated anti-angiogenic mechanisms may well explain the antitumour effects of IFNα [2]. It was clearly demonstrated in these experiments that these anti-angiogenic effects were only mediated by a certain range of relatively low concentrations of IFNα, and were lost at higher dose levels [2]. For such a wide range of biological activities, it has been widely recognised that the dose for optimal biological activity may differ greatly from the maximally tolerated dose. This leads to a difficult position when developing a clinical strategy in the absence of clear surrogate endpoints to identify active doses of IFNα. It has resulted in a great number of empirical trials, each with their own hypothesis on the dose and schedule of IFNα, using patients with a wide range of clinical stages (stages II–IV). This current perspective will provide a short overview of these efforts to identify active treatment schedules with IFNα for stage IV disease as well as discussing the trials where IFN has

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been used in the adjuvant setting for the treatment of malignant melanoma.

2. IFNα in stage IV melanoma: no impact on the response rates or survival

A large number of phase I-II studies have been conducted in an attempt to define the antitumour efficacy of IFNα in stage IV melanoma. A modest antitumour effect was demonstrated with overall response rates varying from 10 to 15%. Of importance is the observation that *no* preferred schedule and/or dose range has emerged from all these studies [1]. This explains the lack of guidance for an evidence-based approach to develop adjuvant therapy and the myriad of trials and the multitude of hypotheses that have been at the basis of these adjuvant trials. Whether the addition of IFNα to other agents could improve outcome in stage IV melanoma has been addressed in a number of phase III trials [3–11]. These trials are summarised in Table 1. The outcome of all these trials is quite disappointing.

A wide dose range of IFN has been explored in these trials from low-dose interferon (LDI) of a flat dose of 3 MU [6] up to high-dose interferon (HDI) schedules of 15 MU/m^2, which amounts to a flat dose of approximately 30 MU [3,7]. It is of note that again there was no indication that HDI mediated a better effect than lower doses. One very small trial comparing dacarbazide (DTIC = D) versus D + HDI in 32 versus 32 patients showed an improved response rate and an impact on overall survival (OS) in the HDI arm [3]. These results were completely anulled, however, by the much larger Eastern Cooperative Oncology Group (ECOG) 3602 trial, reported in 1998, which showed absolutely no improvement in the response rate or median survival. Median survival in the DTIC-alone arm was 10 months, when HDI was added it was 9.3 months, and when HDI was added to DTIC + tamoxifen it was 9.5 months [7]. In the M.D. Anderson Cancer Center trial, the outcome of a very toxic in-house treatment of biochemotherapy with CVD + IFNα + IL-2 showed an improved response rate which translated into a marginally improved survival [11]. Toxicity was considered prohibitive and the benefit was considered doubtful. Moreover, in a similar study at the Surgery Branch of the National Cancer Institute (NCI) comparing chemotherapy with DTIC, cisplatin and tamoxifen to the same combination + IFNα + high-

Table 1
IFNα in phase iii trials in stage IV melanoma

Ref.	Regimen	Pts *n*	RR%	Median survival (months)
[2]	D	32	20	9.6
	D + IFNα (15 MU/m^2)	32	53	17.6
			$P < 0.01$	$P < 0.01$
[4]	D	83	17	8.8
	D + IFNα (9 MU, flat dose)	87	21	7.5
			ns	ns
[5]	IL-2	44	5	10.2
	IL-2 + IFNα (3 MU/m^2)	41	10	9.7
			ns	ns
[6]	D	82	5	11
	D + IFNα (3 MU, flat dose)	84	7	11
	D + IFNα (9 MU, flat dose)	76	8	13
		ns		ns
[7]	D	66	15	10.0
	D + IFNα (15 MU/m^2)	60	21	9.3
	D + T	62	18	8.0
	D + T + IFNα (15 MU/m^2)	62	19	9.5
			ns	ns
[8]	D/BCNU/C/T	30	27	5.5
	D/BCNU/C/T + IFNα (3 MU, flat)/IL-2	35	22	5.0
			ns	ns
[9]	D/C/T	52	27	15.8
	D/C/T/ + IFNα (6 MU/m^2)/IL-2	50	44	10.7
			$P < 0.08$	$P < 0.06$
[10]	C/IL-2	57	16	10.4
	C/IL-2 + IFNα (9 MU, flat dose)	60	25	10.9
				ns
[11]	CVD	92	25	9.5
	CVD + IFNα (5 MU/m^2)/IL-2	91	48	11.8
			$P < 0.01$	$P < 0.06$

D, dacarbazide; C, cisplatin; V, vinblastine; T, tamoxifen; RR, response rate; ns, non significant; Pts, patients; IFNα, interferon-alpha; IL-2, interleukin-2; BCNU, carmustine.

dose IL-2 showed a borderline significant shorter survival rate in the biochemotherapy arm [9]. Overall, it is quite clear that the addition of IFNα to chemo-, immuno- or biochemotherapy does *not* improve response rates or survival.

3. IFNα in the adjuvant setting: a confusing picture

In spite of these observations in stage IV melanoma, IFNα has been extensively studied in the adjuvant setting in the treatment of melanoma. It should be realised that on the basis of the experience in stage IV melanoma, the expectations on the activity of IFNα should have been quite modest. In order to expect a significant impact on minimal residual disease (MRD), there should be evidence that MRD responds in a fundamentally different way (antiangiogenic?) to IFNα or that long-term treatment with IFNα might be active (antiangiogenic?), whereas short-term treatment with IFNα, as is the case in most stage IV melanoma patients, is not.

Moreover, many trials have been underpowered, have used very heterogeneously mixed patient populations (stage II+III), a wide variety of doses and treatment schedules, and have suffered from early and unplanned analyses. Mature data are still pending in some 3000 patients of the overall approximately 6000 patients that participated in the adjuvant trials. With all this heterogeneity, it comes as no surprise that the outcome of these trials has varied in all stages and has varied almost as widely as the dose range employed.

3.1. Reporting by stage and dose of IFN

The adjuvant trials that have been conducted with IFNα can be divided according to the stage of the patient population: stage IIA: thickness primary melanoma >1.5–4.0 mm, clinically node-negative (T3N0M0) or stage IIB: thickness primary melanoma >4.0 mm, clinically node-negative (T4N0M0); and stage III: any primary, lymph node positive (any TN12M0). Moreover, the trials can be divided according to the dose of IFNα that has been evaluated: HDI with doses at 10–20 MU/m^2; intermediate dose IFN (IDI) with doses at 5–10 MU flat doses; and LDI with flat doses at 1–3 MU.

Using this method, the results of the trials with mature follow-up are summarised in Table 2 and the trials with immature follow-up in Table 3. It is important to realise that, of the roughly 6000 patients treated

Table 2
Trials with mature follow-up

Stage II (T3-4N0M0) or IIB (T4N0M0)				Stage III (any TN1-2M0)			
High-dose IFN (HDI)				High-dose IFN (HDI)			
Pts *n*	Trial	DFS	OS	Pts *n*	Trial	DFS	OS
102	NCCTG 20 MU/m^2, i.m., 12 weeks	–	–	160	NCCTG 20 MU/m^2, i.m., 12 weeks	–	–
31	ECOG 1684 20 MU/m^2, i.v., 5 days/week for 4 weeks 10 MU/m^2, s.c., t.i.w. for 48 weeks	–	–	249	ECOG 1684 20 MU/m^2, i.v., 5 days/week for 4 weeks 10 MU/m^2, s.c., t.i.w. for 48 weeks	+	+ at 5 years – at 10 years
112	Intergroup E1690 20 MU/m^2, i.v., 5 days/week for 4 weeks 10 MU/m^2, s.c., t.i.w. for 48 weeks	–	–	314	Intergroup E1690 20 MU/m^2, i.v., 5 days/week for 4 weeks 10 MU/m^2, s.c., t.i.w. for 48 weeks	+	–
Low-dose IFN (LDI)				Low-dose IFN (LDI)			
Pts *n*	Trial	DFS	OS	Pts *n*	Trial	DFS	OS
107	Intergroup E 1690 3 MU, s.c., t.i.w., 2 years	– curve as HDI	–	318	Intergroup E 1690 3 MU, s.c., t.i.w., 2 years	– curve as HDI	–
499	French 3 MU, s.c., t.i.w.,18 months	+	+ at 5 years – at 8 years	427	WHO-16 3 MU, s.c., t.i.w., 3 years	–	–
311	Austrian 3 MU, s.c., t.i.w., 12 months	+	TE				
95	Scottish 3 MU, s.c., t.i.w., 6 months	±					
340	EORTC1887 1/DKG-80 1 MU, s.c., t.i.w., 12 months	–	–	490	EORTC18871/DKG-80 1 MU, s.c., t.i.w., 12 months	–	–

EORTC, European Organization for Research and Treatment of Cancer; NCCTG, North Central Cancer Treatment Group; IFN, interferon; ECOG, Eastern Co-operative Oncology Group; Pts, patients; WHO, World Health Organization; DFS, disease-free survival; OS, overall survival; TE, too early; i.m. intramuscularly; s.c., subcutaneously; i.v. intravenously; t.i.w., 3 times a week.

Table 3
Adjuvant trials with immature follow-up

Pts *n*	Trial	DFS	OS
880	Stage IIB-III	+	+
	ECOG 1694		
	20 MU/m^2, i.v., 5 days/week for 4 weeks		at 1.3 years
	20 MU/m^2, i.v., 5 days/week for 4 weeks		at 1.3 years
	10 MU/m^2, s.c., t.i.w. for 48 weeks		*no control arm
Intermediate-dose IFNα (IDI)			$P<0.046$
1418	Stage IIB-III		
	EORTC 18952	–	TE
	10 MU s.c., 5 days/week for 4 weeks followed by		
	Arm A (10 MU, t.i.w., 1 year)	+	TE
	Arm B (5 MU, t.i.w., 2 years)	*DFMI* $P<0.0145$	at 1.5 years
Low-dose IFNα (LDI)			
	Stage III		
654	UKCCCR	–	–
			at 1.2 years

United Kingdom Co-ordinating Committee on Cancer Research (UKCCCR); DMFI, distant metastasis-free interval. EORTC, European Organization for Research and Treatment of Cancer; NCCTG, North Central Cancer Treatment Group; IFN, interferon; ECOG, Eastern Co-operative Oncology Group; Pts, patients; t.i.w., 3 times a week; i.v., intravenously.

in all of the trials, almost 3000 patients are in the three trials with immature follow-up. Of all the trials with a mature follow-up, there are only two trials with both a significant impact on disease-free survival (DFS) and OS at 5 years follow-up. One trial concerns the evaluation of HDI in high-risk melanoma patients (ECOG 1684 in stage IIB-III) [12] and the other trial evaluates LDI in patients with intermediate risk melanoma (the French Trial in stage II patients) [13]. In both trials, however, the impact on OS is lost at longer follow-up.

3.2. HDI in high-risk melanoma

In the rather small ECOG 1684 trial in 280 patients, a significant benefit on DFS and OS was observed after HDI with IFN-2b for 1 year consisting of 4 weeks daily intravenous (i.v.) administration of 20 MU/m^2, followed by 48 weeks of 10 MU/m^2, subcutaneously (s.c.), 3 times a week (t.i.w.) [12]. This result was not sustained. The impact on OS was lost with a longer follow-up and the next Intergroup trial E1690 showed only a marginal effect on DFS with HDI and no effect at all on OS ($P=0.995$) [14]. HDI failed to have a significant impact in the NCCTG Trial (262 patients). Here the same high dose when administered intramuscularly (i.m.) t.i.w., for only 12 weeks, had no significant impact on survival in this mixed population of stage II patients with primaries thicker than 1.7 mm and stage III melanoma patients [15]. Both HDI regimens in these three trials were associated with serious toxicity with grade III-IV toxic events in approximately 75% of the patients, requiring dose reductions and interruptions of the treatment schedules. A fourth trial containing a HDI-arm in stage IIB-III melanoma patients has been reported very recently. The Intergroup 1694 trial was unblinded early and reported early [16] because of a significant difference for both DFS, as well as OS, between the HDI arm and the ganglioside-vaccine arm in the 774 randomised stage IIB-III patients. These differences were reported after a median follow-up of only 1.3 years, which makes it virtually impossible to make any solid claims about the impact on OS. Thus, whether these differences in survival will continue to be significant needs to be confirmed, especially in light of the Intergroup E 1690 and the ECOG 1684 experience. In a pooled analysis of the trials 1684 and 1690, presented at the 37th meeting of the American Society of Clinical Oncologists (ASCO) in 2001, the impact on OS by HDI was not so evident when one realises that 198 patients in the observation arms of 1684/1690 had died thus far, whereas 201 patients had died in the HDI arms [17].

3.3. LDI in high-risk melanoma

LDI-treatment was evaluated in the World Health Organization (WHO)-16 trial. In this trial, 427 stage III melanoma patients were evaluable after randomisation into either the observation arm or the LDI-treatment arm (3 MU, s.c., t.i.w., for 3 years). Although a temporary effect on DFS was observed in the treatment arm [18], in the final analysis no DFS or OS benefit was observed in the WHO-16 trial [19]. LDI treatment at 3MU for 2 years, in the ECOG 1690 trial did show an impact on DFS similar to HDI, but this was statistically non-significant [14]. This, despite the fact that the DFS curve was superimposable on the HDI arm of the E1690 study, which had a borderline impact on DFS. Just like HDI, LDI did not have an impact on OS. The recently

reported early results on LDI in stage III patients in the UK trial revealed no impact on either DFS or OS [20]. Another low dose IFNα, (1 MU, s.c., on alternative days for 1 year) regimen was evaluated in the EORTC-18871 trial. At this ultra-low dose of IFNα, no effect was shown on either the DFS or OS rates (96). Overall, there is no evidence that treatment with IFNα at flat doses of 1–3 MU, s.c., t.i.w. has an impact on DFS or OS in high-risk melanoma patients [21].

3.4. HDI in intermediate-risk melanoma

The track record of HDI in stage II melanoma patients is very inconsistent. The NCCTG trial which evaluated the impact of high-dose IFN, intramuscularly, t.i.w. for 3 months was negative both for DFS and OS in the stage II population of this mixed stage II–III trial [15]. Moreover, both the ECOG 1684 and ECOG 1690 did not show a significant impact of HDI on DFS or OS in the stage IIB population of these trials [12,14]. In the Intergroup 1694 trial, HDI had a significant impact in the stage IIB population on DFS, but not on OS at early analysis [16]. Overall, the results are quite inconsistent and do not support the use of HDI in intermediate-risk melanoma patients.

3.5. LDI in intermediate-risk melanoma

In stage II patients with primary melanomas >1.5 mm, clinically node-negative, three trials in Europe have completed accrual. These three trials are all similar in design, all using IFNa2a at low doses of 3 MU for 6 months (Scottish trial), 12 months (Austrian trial) or 18 months (French trial). The recent report on the Scottish trial has shown a temporary benefit on the DFS and OS rates [22], whereas the use of 12 months in the Austrian Trial has been reported to result in a significant benefit on the relapse rate [23]. The Austrian study has not reached maturity and so far no significant impact on OS has been observed. The French trial has reached maturity and a significantly prolonged DFS was observed in the IFNα-arm. The impact on OS failed to reach significance, but demonstrated a favourable trend in the initial report [13]. At longer follow-up, however, it has become clear that the significant impact on OS at 5 years follow-up achieved in the French trial was lost at 8 years. In the ECOG 1690 trial, a borderline effect on DFS was observed in the LDI arm but no effect on OS was observed in the stage IIB patients. Also, in the EORTC/DKG-80 trial, the very low dose of 1 MU, s.c., t.i.w. for 1 year had no impact on DFS or OS in stage II patients [21]. So far only one trial has reported an impact on OS [13] and two trials a significant impact on DFS, whilst two more trials reported a temporary or borderline impact on DFS [22,23]. The ultra-low dose of 1 MU was not associated with any effect on the DFS or OS rates [21]. With the consistent phenomenon of a modest impact on DFS in most trials with IFNα at 3 MU, s.c., t.i.w., but without a consistent impact of LDI on the OS rate, the use of LDI in the adjuvant setting in patients with intermediate-risk melanoma can not be considered advisable or the standard of care. Here, it must be realised that more than 80% of the relapses in stage II patients are composed of clinical evidence of regional lymph node metastases. These manifestations will become almost extinct in the near future due to sentinel node (SN) staging of stage II patients. The absence of an impact of LDI on OS should therefore be recognised as the main reason to conclude that LDI cannot, and should not, be considered the standard of care for stage II melanoma patients.

3.6. Intermediate-dose IFNα (IDI)

The largest trial by far in high-risk melanoma patients (stage IIB-III) is the EORTC 18952 trial in 1418 patients. This trial evaluates the impact of intermediate doses of IFN where after an induction period of 4 weeks, 5 days/week, 10 MU, s.c. is followed by a maintenance period of 10 MU, s.c., t.i.w. for 1 year versus 5 MU, s.c., t.i.w., for 2 years versus observation. The first analysis from the EORTC 18952 trial was reported at the 37th Annual Meeting of ASCO [21]. The analysis indicates that the duration of treatment is more important than the dose of IFNα, since the higher dose of 10 MU for 1 year had no significant impact on the distant metastasis-free interval (DMFI), the primary endpoint in this trial, whilst the lower dose of 5 MU for 2 years showed a significant impact on the DMFI ($P=0.0145$) [21]. Again, these data should be interpreted with the greatest caution as many 'early positive reports' have subsequently proved negative. Yet these results support the trial design of the currently ongoing EORTC 18991 trial, which evaluates the impact of long-term maintenance therapy of 5 years with pegylated-IFNα (PEG-Intron) compared with observation in 900 stage III patients. The mature results of the EORTC 18952 trial on IDI are awaited with great interest, as IDI has an acceptable toxicity profile (approximately 10% grade III-IV toxic events, in contrast to 78% with HDI). If the reported early impact on DMFI translates into an OS benefit, IDI may, because of its acceptable toxicity profile, be considered as a reasonable candidate for adjuvant therapy in high-risk melanoma patients.

3.7. Ongoing trials with IFNα

The early results of the EORTC 18952 trial and on the basis of the results with IFNα in stage II patients (French, Austrian and Scottish trials) and the observation of a rebound in the relapse rates in the IFNα-treated patients in a number of trials (WHO-16 trial in stage

III patients, French trial in stage II patients) the hypothesis has been raised that IFNα needs to be administered for very long periods of time in order to be effective. This hypothesis is also based on the anti-angiogenic mode of action of IFNα, as demonstrated by Fidler and others [2,24]. Therefore the EORTC-Melanoma Cooperative Group will evaluate long-term therapy with IFNα against the standard of care (observation) in stage III melanoma. Long-term therapy has two prerequisites: low toxicity and easy administration. Therefore a well tolerated dose of the pegylated form of IFNα will be evaluated, as this agent needs only to be administered s.c. once a week, for a total treatment period of 5 years. This trial (EORTC 18991) has been activated in July 2000. Roughly 50% of the total population of approximately 900 patients are expected to enter the trial as patients with microscopic metastatic involvement of regional lymph node(s) as a consequence of the steady increase in SN mapping in Europe. The other 50% will be patients with clinically overt (palpable) regional node involvement. Side studies regarding the value of reverse transcriptase-polymerase chain reaction (RT-PCR) of the SN and other nodes in the regional node basin and of RT-PCR of blood samples will provide further insight into the biological importance and predictive value of such procedures. In this respect, one must signal that the first report on the predictive value for relapse on the basis of RT-PCR on the SN, by the group of Reintgen of the Lee Moffit Cancer Center are very promising and convincing [25].

Because of SN staging, the prognosis of SN-staged node-negative stage II patients has improved enormously [26]. This stage migration has led to the position in the EORTC that IFNα is an agent that is associated with too much toxicity to be evaluated in this population [27]. Therefore, stage II patients are randomised between vaccination with GM2-KLH/QS-21 versus the standard of care (observation) in the EORTC 18961 trial (1300 patients).

The US-Intergroup is evaluating in trial ECOG 1697 the impact of 4 weeks of IFN, 20 MU/m^2, i.v., for 4 weeks versus observation in 1420 patients. These huge numbers of patients are necessary because of the tremendous impact of SN mapping and the excellent prognosis of SN-negative patients. In the USA, two more very large adjuvant trials are ongoing. The Sunbelt trial evaluates the impact of SN staging and the use of RT-PCR methods on SN evaluation, and HDI (ECOG 1684 schedule) in a multi-arm trial in 3000 patients [28]. Morton's Polyvalent Melanoma Cell Vaccine (PMV), a melanoma cell line-based vaccine that thus far has only been studied in uncontrolled trials [29] is now being evaluated in a large multicentre trial in 750 stage III patients. Bacillus Calmette Guérin (BCG) + PMV treatment will be compared with treatment with BCG alone.

4. Conclusions

IFNα has only a modest activity in melanoma. In stage IV metastatic melanoma, there is no evidence that adding IFNα to chemotherapy or biochemotherapy improves the response rates or survival. This represents a difficult starting point for the development of an effective adjuvant therapy. In the adjuvant setting, results are heterogenous and inconsistent, reflecting its modest activity, which overall translates into an impact on relapse-free survival, which can be seen with various doses of IFNα, but no proof of a significant impact on survival [30]. Given the broad profile of dose-dependent toxicity, there is a quest for a tolerable dose with an effect that overrules the negative effects of IFNα. It may be time for a change of paradigm such as exploring the anti-angiogenic activities of IFNα in non-toxic long-term treatments.

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