Adjuvant therapy of cutaneous melanoma: the interferon debate

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Despite the use of a variety of cytotoxic and immunotherapeutic agents in adjuvant trials in patients following resection of high-risk early cutaneous melanoma, only interferon-α2b (IFN-α) has shown reproducible efficacy. High-dose IFN-α (HDI) is superior to observation in prolonging relapse-free survival. There is still no formal proof of a statistically significant advantage of HDI in prolonging overall survival. For this reason the continued use of observation-only control arms is justified and desirable in adjuvant melanoma trials, and, wherever possible, patients with resected high-risk and intermediate-risk melanoma should be entered on these studies. The toxicity of HDI is high, but the majority of patients complete treatment with dose modification and nearly all toxicity is rapidly reversible. There is now a useful body of information on the supportive care of patients receiving HDI, and data on cost and quality-adjusted time without symptoms and toxicity (Q-TwiST) to support its use in certain high-risk patients. Interim results from a trial of intermediate-dose IFN-α are promising. These, and ongoing studies of pegylated IFN-α, and of shorter induction-only HDI promise refinements in treatment which may improve efficacy-toxicity ratios.

**Key words: adjuvant therapy, interferon-α, melanoma**

Introduction

Few aspects of the modern treatment of cutaneous melanoma (‘melanoma’) have provoked such controversy as the interpretation of clinical trials of interferon-α (IFN-α) in the adjuvant treatment of high-risk disease following surgery. Partly, this has been engendered by the high hopes attached to the early demonstration of the antitumour effects of IFN-α; partly, it derives from the frustration and impotence experienced by oncologists in their endeavours to find effective systemic treatments for this disease. Additionally, it has been fuelled by the wide variability in the results of successive randomised controlled trials of high-dose IFN-α (HDI) the first of which demonstrated a significant benefit over observation in overall survival (OS), a finding never subsequently repeated. Consequently, a trans-Atlantic divide has ensued, with North American proponents declaring HDI ‘standard therapy’ for high-risk melanoma patients [1, 2], whereas European oncologists, analysing the same data, state that the routine use of IFN-α cannot be recommended outside the scope of clinical trials [3]. The increasing maturity of the clinical trials of IFN-α conducted in the 1980s and 1990s, together with recent meta-analyses, provide an opportunity to revisit this question and attempt to adjudicate in this ongoing clinical debate.

The challenge of adjuvant treatment of melanoma

Melanoma remains a major public health problem. The lifetime incidence in New South Wales, Australia, is one in 25 for men and one in 36 for women, making melanoma the fourth most common cancer in men, and the third most common in women [4].

Patients presenting with AJCC (American Joint Committee on Cancer) stage I melanoma have an excellent prognosis (Table 1) and are not generally considered for systemic adjuvant treatment. However, a significant number of patients present each year with disease categorised as high risk (<50% 10 year survival) and intermediate risk (51–64% 10 year survival). By these criteria, patients with stage IIA, IIB and IIA disease could be regarded as at intermediate risk, while those with IIC, IIB and IIC disease are at high risk (Table 1). In the revised AJCC staging series, 29% of the 17600 patients fell into the intermediate-risk category, and 7% into the high-risk group [5]. A recent audit of Sydney Melanoma Unit data for 2002 reveals ~8% of patients to be stage III and 3% to be stage IIC at presentation (Helen Shaw, personal communication).

Changes in staging and the impact of sentinel node biopsy

All published adjuvant trials in melanoma have used the older (1977) AJCC/UICC (Union Internationale Contre le Cancer) staging system. Major changes have now been incorporated to remove significant heterogeneity within certain staging groups, and to incorporate the important additional prognostic information contributed by sentinel node biopsy (SNB) [5]. These changes include reclassifying T groups by depth, inclusion of ulceration to define Tb subgroups, reclassifying T4 tumours as stage II (not stage III), the use of nodal number and the inclusion of microscopic nodal classifications. The impact of this system is
considerable stage migration. The importance of this is two-fold. Firstly, the heterogeneity in prognosis contained within previously stratified subgroups in adjuvant trials may account for some of the variation in outcomes between trials. Secondly, it is critical that future trials utilise the full information available from SNB in trial design.

Interferon biology

The interferons are a group of naturally occurring cellular cytokines with important physiological functions in antiviral and antitumour defence. They were first described in 1957 by Isaacs and Lindenmann [6] and shortly afterwards were shown to display antitumour activity in experimental systems. The interferons were initially classified according to their separation on HPLC (high pressure liquid chromatography) profiles into α, β and γ types. Later it became evident that IFN-α was produced principally by leukocytes, IFN-β by fibroblasts and IFN-γ by immune cells. Induction of production follows exposure of the producer cells to viruses, double-stranded RNA, polypeptides or cytokines [7, 8]. The interferons bind to cell surface receptors which, after oligomerisation, initiate a cascade of phosphorylation reactions in JAK–Stat signalling intermediates, ultimately activating transcription of IFN-stimulated genes (ISGs) [8, 9]. Expression of ISGs has a variety of cellular effects. In the case of IFN-α, relevant antitumour effects include direct cytotoxic and cytostatic effects on tumour cells, antiangiogenic effects, increased expression of MHC (major histocompatibility complex), tumour-specific antigens and adhesion molecules. In addition, stimulatory effects are seen in T cells and natural killer cells [8, 9]. Recombinant IFN-α is produced by two pharmaceutical companies. IFN-α2a (Roferon A; Roche Laboratories, Nutley, NJ, USA) and IFN-α2b (Intron-A; Schering-Plough, Kenilworth, NJ, USA) have molecular sequences that differ from one another by a single amino acid at position 23 [10]. The majority of adjuvant trials in melanoma have been conducted using IFN-α2b.

Activity of interferon against advanced melanoma

Following the demonstration of IFN-α activity against murine B16 melanoma cell lines in vitro and in vivo [11], clinical trials of the agent were conducted. Overall response rates for single agent IFN-α in metastatic melanoma were ~15%, with ~5% complete remissions [12]. There was no clear benefit for different doses in the range 10 million Units (MU) three times per week to 50 MU daily. Responses appeared to be more durable than those occurring for dacarbazine alone [13], but there was no additional benefit in the advanced disease setting for combinations of dacarbazine plus IFN-α over single agent dacarbazine [14].

High-dose interferon-α2b as adjuvant treatment for melanoma

Efficacy

The use of a HDI regimen for adjuvant treatment of melanoma was pioneered by Kirkwood et al. [16]. The most commonly used protocol employed an initial induction phase of 20 MU/m² i.v. daily for 5 days each week for 4 weeks, followed by a maintenance phase at 10 MU/m² s.c. three times a week for 48 weeks (total treatment duration of 52 weeks). The rationale for the initial high-dose i.v. treatment phase was to provide maximal dose intensity and minimise the induction of anti-IFN antibodies. The five trials utilising HDI are summarised in Table 2.
**Table 2. Clinical trials of high-dose IFN-α2b**

<table>
<thead>
<tr>
<th>Trial</th>
<th>IFN-α2b dose</th>
<th>Control</th>
<th>No. of patients</th>
<th>Median FU</th>
<th>RFS</th>
<th>OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCTG 83–7052</td>
<td>20 MU/m² i.m. 3× a week for 3 months</td>
<td>Observation</td>
<td>262</td>
<td>6.1 years</td>
<td>– (+ for LN+ subset only)</td>
<td>–</td>
<td>[15]</td>
</tr>
<tr>
<td>ECOG E1684</td>
<td>20 MU/m² i.v. 5 days per week for 4 weeks, 10 MU/m² s.c. 3× a week for 48 weeks</td>
<td>Observation</td>
<td>287</td>
<td>6.9 years</td>
<td>+ at 6.9 years, (P = 0.0023) + at 6.9 years, (P = 0.00237)</td>
<td>–</td>
<td>[16]</td>
</tr>
<tr>
<td>Intergroup E1690</td>
<td>20 MU/m² i.v. 5 days per week for 4 weeks, 10 MU/m² s.c. 3× a week for 48 weeks</td>
<td>Observation, LDI (3 MU s.c. 3× a week)</td>
<td>642</td>
<td>6.2 years</td>
<td>+ (HDI), (P = 0.054) –</td>
<td>–</td>
<td>[17]</td>
</tr>
<tr>
<td>Intergroup E1694</td>
<td>20 MU/m² i.v. 5 days per week for 4 weeks, 10 MU/m² s.c. 3× a week for 48 weeks</td>
<td>GMK vaccine</td>
<td>774</td>
<td>1.9 years</td>
<td>+ (P = 0.0025) +</td>
<td>+</td>
<td>[18, 19]</td>
</tr>
<tr>
<td>ECOG 2696</td>
<td>20 MU/m² i.v. 5 days per week for 4 weeks, 10 MU/m² s.c. 3× a week for 48 weeks</td>
<td>GMK vaccine</td>
<td>107</td>
<td>2.0 years</td>
<td>+ (P = 0.016; P = 0.03)</td>
<td>–</td>
<td>[19, 21]</td>
</tr>
</tbody>
</table>

**ECOG 1684.** The ECOG (Eastern Cooperative Oncology Group) 1684 trial enrolled 287 patients with (old) AJCC stage IIB or III disease (T >4 mm, lymph nodes +/-; any T, pathological lymph nodes +; regional lymph node recurrence). Patients all received regional lymphadenectomy. Patients were randomised between: (i) those receiving HDI (20 MU/m² i.v. for 5 days each week for 4 weeks, followed by ‘maintenance’ therapy of 10 MU/m² s.c. three times weekly for a further 48 weeks); and (ii) observation. At median follow-up of 6.9 years, both relapse-free survival (RFS) and OS were significantly better for the HDI arm (RFS 1.72 versus 0.98 years, \(P = 0.0023\); OS 3.82 versus 2.78 years, \(P = 0.0237\)). Five-year estimated RFS was improved by 11% [16]. Recently, a mature update of this study has been analysed at a median follow-up of 12.6 years. In this analysis, the improvement in RFS (which is equivalent to metastasis-free survival, as all patients sustained lymphadenectomy) persists, with 34 alive relapse-free in the observation arm and 51 in the treated arm (\(P = 0.01\)). The difference in OS disappeared, however (\(P = 0.09\) [17]), an effect at least in part attributed to the fact that participants in this trial are now entering their seventh decade, the median age at entry having been 49 years [17]. An independent analysis of E1684 also failed to show a statistically significant benefit in OS [22], although the statistical methods in this analysis have been challenged [23]. The gain in median survival for recipients of HDI in the updated analysis was 13.8 months (45.8 months with HDI compared with 32 months for observation).

On the basis of the data at 6.9 years the FDA (US Food and Drug Administration) approved the use of IFN-α2b for (old AJCC) stage IIB and III melanoma.

**Intergroup E1690.** In this three-arm trial, 642 similar patients (608 eligible) were randomised following wide local excision (but not mandatory lymph node dissection) between: (i) the same HDI regime as ECOG 1684; (ii) 2 years of low-dose IFN-α2b (LDI), 3 MU s.c. three times per week; and (iii) observation. At 52 months median follow-up, an advantage in 5-year estimated disease-free survival was again seen for HDI (44% versus 35%, \(P = 0.054\) but not for LDI (40%). There was, however, no advantage in OS for HDI (52%) or LDI (53%) over observation (55%). At 74 months, there had been 108 deaths in the HDI arm and 103 deaths in the observation arm of this study [19].

The failure of E1690 to replicate the advantages seen for HDI in E1684 has been attributed to the marked improvement in 5-year OS in the observation arm, which was 55% for E1690 compared with just 37% for E1684 (\(P = 0.001\)) [18]. The investigators have explained this difference on the basis that 37 of 121 patients relapsing on the observation arm of E1690 received salvage HDI, comprising all but one of the patients relapsing in resectable regional lymph nodes. In this non-randomised setting, in which considerable selection bias may have occurred, patients receiving salvage therapy had a prolonged survival compared with those who did not (2.2 years versus 0.8 years, \(P = 0.0024\)). However, the improvement in survival of untreated (old AJCC) stage II and III patients is a phenomenon observed internationally between 1980 and 2000 (Figure 1). Factors involved may have included better surgery and more accurate staging in later years, or there may have been some unexplained changes in natural history.

Further explanations for the lack of benefit of HDI in E1690 include the fact that patients with T4cN0 disease were eligible in E1690, whereas all patients in E1684 had undergone lymphadenectomy.

**Intergroup E1694.** In this study, a comparison was made between HDI (by then regarded by the trialists as ‘standard of care’) in one arm and an experimental ganglioside vaccine, GMK, in resected stage IIB/III patients. GMK consists of a well-defined melanoma antigen, GM2, conjugated to keyhole limpet hemocyanin (KLH)
and administered with the adjuvant QS-21 for 96 weeks. Of 880 patients entered, 774 were eligible for analysis. The trial was closed after interim analysis indicated the inferiority of GMK compared with HDI. At a median follow-up of 16 months, OS in the HDI arm was 78% compared with 73% in the GMK arm \((P = 0.009)\). Two-year disease free survival was 62% and 49%, respectively \((P = 0.0015)\). HDI was associated with a treatment benefit in all subsets of patients with zero to greater than or equal to four positive nodes, but the greatest benefit was observed in the node-negative subset \(\text{RFS hazard ratio} = 2.07; \text{OS hazard ratio} = 2.71\).

**ECOG E2696.** This small trial, designed to pilot combinations of HDI and the vaccine GMK, compared two combinations of HDI and the vaccine GMK (one concurrent and the other sequential) against GMK vaccine alone in 107 high-risk melanoma patients with resected stage IIB, III or IV disease, in a randomised phase II design. Although relapse and death were not primary end points of the study, Kaplan–Meier distributions of OS and RFS were estimated at a median follow-up of 24 months, and demonstrated a benefit in RFS for the two HDI-containing arms, compared with the vaccine-only arm \((P = 0.016; P = 0.03)\) [21]. There was no benefit in OS.

**Discussion of high-dose interferon/vaccine trials**

The main question about the studies comparing HDI with vaccine concerns the possibility that the vaccine had a deleterious effect on survival.

The main arguments against a deleterious vaccine effect are the following: (i) the antibody response to GMK had previously been demonstrated to correlate with improved survival [24], and patients on the vaccine arm of the E1694 trial who demonstrated antibody responses at 1 month had a strong trend towards improved survival compared to non-antibody responders; (ii) the pooled data from vaccine arms had an improved survival compared with pooled data from observation arms in all HDI trials [19] (however, as described above, such historical comparisons are notoriously difficult in high-risk melanoma); (iii) the hazard ratios for improved RFS on HDI were similar for E1694, E1690 and E1684; (iv) there was no evidence of any detrimental effect of vaccination with GM2 plus BCG in a previous randomised trial [24].

Notwithstanding these arguments, concern that the GMK vaccine may have been detrimental remains. An important precedent for deleterious effects of vaccines in adjuvant cancer trials comes from the meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group (‘Oxford overview’) of adjuvant therapy for early breast cancer in which 11 of 24 immunotherapy trials showed a worse outcome for the immunotherapy arm compared to observation [25]. There is at least a theoretical possibility that antigenic vaccines could induce tolerance, or T-cell anergy, particularly when tumour-associated antigens are presented in the absence of costimulatory molecules. The end result could be a negative therapeutic effect.

One important suggestion that the vaccine was indeed deleterious in this study is the fact that the Kaplan–Meier plot of survival on GMK compares very closely with that of the observation arm on the E1690 study, despite the fact that the HDI arm showed a substantially better survival over that of identically staged and treated patients on E1690 (Figure 2). It is difficult to explain this similarity unless, in fact, there was a deleterious effect of vaccine therapy on the survival of these patients.

Concerns have also been raised about a possible unequal distribution of patients with occult lymph node involvement amongst the 141 T4N0M0 patients with no lymph node surgery who were included in the study [26]. An over-inclusion of SNB-negative patients in the HDI arm could significantly prejudice survival benefits in that arm.

**Pooled analyses of high-dose interferon trials**

Pooled data for the 1915 patients entered on the four ECOG/Intergroup adjuvant trials of HDI shown in Table 2 were re-analysed in 2001 with a median overall follow-up of 75 months (33 months for those alive) [19]. These data revealed median RFS of 1.4 years for observation, 3.0 years for HDI and 2.1 years for GMK vaccine, with significance values of \(P = 0.05\) (HDI versus vaccine) and \(P = 0.01\) (HDI versus observation) (log rank test). Median OS was 4.1 years for observation, 6.2 years for HDI and 3.8 years for vaccine, with \(P = 0.69\) (HDI versus vaccine),
P = 0.01 (HDI versus observation). The main problems with this particular pooled analysis are the heterogeneity between the trials being compared in terms of stage of disease and trial design, and the lack of maturity of the E1694 and E2696 trials which heavily influence the positive outcome.

A more formal meta-analysis of HDI trials was also performed, using only published trials with an observation control arm, and therefore excluding E1694. This analysis showed no significant effect of HDI on OS (12% reduction in mortality odds ratio, standard deviation 8, 2P = 0.1), but a significant effect on RFS (24% reduction in odds ratio of recurrence, standard deviation 7, 2P = 0.0009) [27].

A review of a number of selected HDI trials, including three of those summarised in Table 2, showed no evidence of benefit in OS [22]. However, there was such heterogeneity between the trials that a formal meta-analysis was not possible, and the large E1694 trial was not included.

**Toxicity**

Given general agreement about benefits in RFS there would probably be little debate about the use of HDI as adjuvant treatment for high-risk early melanoma were it not for the high incidence of disabling toxicity, particularly during the i.v. induction phase of the treatment protocol. This phase has been judged to be an essential element in the treatment schedule because the separation of Kaplan–Meier curves of RFS occurs very early. The major toxicities and reported incidence have been reviewed elsewhere [23] and are shown in Table 3. The most prominent acute features are those of an influenza-like syndrome with constitutional features including fever, rigors, headache and myalgia. In most studies, ECOG grade 3 and 4 toxicities are noted in approximately one-third of patients [23], but most toxicity is rapidly reversible on cessation or dose reduction.

Dose reduction during HDI therapy was necessary in 33–58% of patients during induction and 38–59% of patients during the maintenance phase of the E1684, E1690 and E1694 adjuvant trials [28], but the lower figure was achieved in the latest study, suggesting increasing clinical skill in ameliorating toxicities. With appropriate dose modification >80% of patients were able to complete 12 months of therapy on the E1694 trial [23]. Nonetheless, in the E1684 and E1690 trials, toxicity classified as ‘severe’ was experienced by 67.1% and 52.6% of patients, respectively, for a mean of 7.3 months [29].

Considerable skill has been accumulated in the nursing care of patients on HDI, and in the symptomatic relief of acute toxicity. This includes the administration of HDI late in the day, the liberal use of paracetamol and non-steroidal anti-inflammatory medication to relieve fever and myalgia [30], and the use of prochlorperazine, metoclopramide and ondansetron or granisetron for nausea and emesis. Fluid support is important to prevent dehydration [23]. The routine prophylactic use of antidepressants like paroxetine has been shown to prevent serious depressive reactions [31–33], and mood stabilisers such as gabapentin have also been advocated [34]. Fatigue can be alleviated in certain cases using supportive elements such as light exercise, nutritional care, encouragement of non-caffeine containing fluids and, in some cases, the use of megestrol acetate and, in severe cases, methylphenidate. The latter is the subject of a current randomised controlled clinical trial by ECOG. Corticosteroids, which would potentially relieve many of the side-effects of HDI, are contra-indicated because of potential interference with the immune mechanisms of IFN-α action, and demonstrated abrogation of antitumour effects of IFN-α in animal models.

HDI induces inhibition of up to 60% of the cytochrome P450 enzyme isozymes in the liver, and the degree of inhibition correlates with gastrointestinal, neurological, haematological and influenza-like toxicities [28]. These enzymes are responsible for the metabolism of many agents used in the treatment of these

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute toxicity</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Common</td>
</tr>
<tr>
<td>Rigors</td>
<td>Common</td>
</tr>
<tr>
<td>Headache</td>
<td>Common</td>
</tr>
<tr>
<td>Nausea</td>
<td>Common</td>
</tr>
<tr>
<td>Emesis</td>
<td>Occasional</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Common</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Common</td>
</tr>
<tr>
<td>Supraventricular tachyarrhythmias</td>
<td>Rare</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Common</td>
</tr>
<tr>
<td>Hepatic enzyme elevation</td>
<td>Common</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>Occasional</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Rare</td>
</tr>
<tr>
<td>Chronic Toxicity</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Common</td>
</tr>
<tr>
<td>Depression</td>
<td>Common</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
<td>Common</td>
</tr>
<tr>
<td>Coma</td>
<td>Rare</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Rare</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Common</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Common</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Occasional</td>
</tr>
<tr>
<td>Intestinal nephritis</td>
<td>Rare</td>
</tr>
<tr>
<td>Hyper-triglyceridemia</td>
<td>Occasional</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>Occasional</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Rare</td>
</tr>
<tr>
<td>Retinal microvascular changes</td>
<td>Rare</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Occasional</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>Common</td>
</tr>
</tbody>
</table>

*Patients with a history of psychiatric illness should be managed in collaboration with an experienced psychiatrist [23].

*High-dose interferon-α treatment may be contraindicated in the presence of severe psoriasis [23].

Table 3. Toxicity of high-dose interferon-α
patients, including most antidepressants, codeine, benzodiazepines and warfarin. Substantial dose modification may be necessitated by these potential drug interactions.

Acute hepatic transaminitis is common, and normally reversible on dose reduction or cessation. Rarely, fatal hepatic necrosis has followed the administration of IFN-α in spite of abnormal liver function tests [16]. However, there have been no toxic deaths on cooperative group studies of HDI since the introduction of formal dose modification guidelines [23].

With maintenance therapy, more chronic toxicities become apparent, including anorexia, malaise and weight loss. These later toxicities are complex results of dysgeusia, low-grade fever and nutritional compromise. Thyroid dysfunction and possible autoimmune processes may also contribute [12].

Time without symptoms and toxicity. An analysis of quality-adjusted time without symptoms and toxicity (Q-TwiST) was performed for the E1684 trial of HDI versus observation [35]. The HDI group had more quality-of-life-adjusted time than the observation group regardless of the relative valuations placed on time with toxicity and time with relapse. There was a mean gain of 8.9 months without relapse ($P = 0.03$) and 7 months of OS time ($P = 0.02$) for the HDI patients after 84 months of follow-up as compared with the observation group. This gain was significant ($P < 0.05$) for patients who consider time with toxicity to have a high relative value and time with relapse to have a low relative value. In contrast, for patients who valued time with toxicity as being similar to time with relapse, the quality-adjusted gain for HDI was not statistically significant. An analysis stratified according to tumour burden indicated that the benefit of HDI was greatest in node-positive patients. These data are heavily influenced by the highly significant differences in RFS and OS seen in the seminal E1684 study.

In a further attempt to quantify the trade-offs between HDI toxicity and survival, Kilbridge et al. assessed patient utilities for health states associated with IFN-α2b therapy in 107 low-risk melanoma patients who were not receiving adjuvant treatment [36]. At least half the patients were willing to tolerate mild/moderate and severe toxicity from HDI for 4% and 10% improvements, respectively, in 5-year disease-free survival. It should be noted that only the E1684 trial demonstrated an improvement with HDI in 5-year RFS of $>10\%$ (26% versus 37%). However, in a further study of quality-of-life-adjusted survival (QAS) in E1684, IFN-α resulted in an increase in QAS for all sets of patient utilities, however this only reached significance for 16% of patients; using E1690 data, 77% of patients experienced a benefit in QAS from IFN-α and 23% experienced a decrease in QAS, and neither of these effects was statistically significant [29].

Cost-effectiveness

The cost-effectiveness of HDI was evaluated, based solely on the significantly positive E1684 trial [37]. In this trial, the cost of HDI per life-year gained ranged from US$13700 after a projected 35 years to US$32600 at 7 years (the median follow-up of E1684). The benefits of IFN-α2b projected over a lifetime yielded incremental cost per life-year or quality-adjusted life-year that were <US$16000. This compares favourably with other accepted adjuvant therapies of breast and colorectal cancer. It must be re-emphasised, however, that E1684 is the only trial that has shown an OS benefit of HDI versus observation, and there has been no re-analysis of cost-effectiveness against recent updated follow-up of this trial at 12.6 years in which the OS benefit has disappeared [17].

HDI: what should oncologists advise their high-risk patients?

Ideally, patients with high-risk primary melanoma should be entered on clinical trials that are attempting to answer critical questions regarding longevity, quality of life and treatment costs. As no agent has been demonstrated definitively to prolong OS for any group with high-risk disease it is desirable and ethical to include an observation arm in the design of these trials, even for node-positive groups.

For patients outside of clinical trials observation, not HDI remains the standard of care, as OS remains the key end point for adjuvant therapy. However, patients without significant comorbidity or contraindications to HDI deserve a full explanation of the controversy regarding its use, including the fact that all analysts are agreed that it is the only agent showing activity against melanoma in the adjuvant setting and that it prolongs 5-year RFS by $\sim 10\%$ at the expense of considerable, but rapidly reversible, toxicity. The meta-analysis of HDI trials showed a 24% reduction in the odds of recurrence for IFN-α treated patients ($2P = 0.0009$) [27]. A decision rule derived from that proposed by Kilbridge et al. [29] may assist clinicians in helping patients make a decision regarding HDI: treat a patient with HDI if he or she agrees with the statement, “If I had a serious disease, I would gladly accept feeling lousy for a year if it improved my chances of having a longer period without the disease”, and if he or she answers ≤10% to the following statement, “I would put up with the side-effects of HDI treatment only if it decreased the chance of the melanoma returning in 5 years time by at least x%”. Many such patients choose an attempt at HDI on the clear understanding that they are free to abandon it at any point if toxicity is prohibitive.

It is imperative that HDI be administered strictly according to guidelines, and that dose reductions are only carried out as specified for the more recent ECOG/Intergroup trials, and summarised recently by Kirkwood [23]. There may be a temptation for clinicians treating patients off study towards leniency in dose modification for the common toxicities of fatigue and influenza-like syndrome. More generous dose reductions than those used in published trials could result in a substantial reduction in any beneficial effect on RFS.

Low and intermediate dose interferon-α2b

The use of low- and medium-dose IFN-α2b as adjuvant treatment of melanoma has been reviewed elsewhere [1–3]. Some trials have demonstrated a delay in recurrence for IFN treated arms in these trials, and a meta-analysis showed a 13% reduction in the odds of recurrence for patients treated with low-dose IFN-α, but
no difference in OS [27]. It is likely, however, that this benefit is confined to stage IIB patients, and important prognostic factors such as sentinel node status and primary tumour ulceration were not routinely evaluated.

The EORTC (European Organisation for Research and Treatment of Cancer) have recently performed a preliminary analysis on their 18952 trial which compares IFN-α2b at 10 MU s.c. three times per week for 1 year with 5 MU s.c. three times per week for 2 years and with an observation alone arm. These doses are approximately half the total accumulated IFN-α2b dose on the HDI trials. This preliminary analysis showed an improvement for distant metastasis-free survival for the 2-year IFN arm ($P = 0.0145$), with acceptable toxicity (10% grade 3 or 4) [38]. Distant metastasis-free survival is a potential surrogate for OS, as it overcomes the confounding effect of locoregional recurrence, for which there is a salvage rate of $\sim 30\%$.

**Future directions**

Existing refinements in staging, including the use of sentinel node biopsy and the use of tumour ulceration as a prognostic factor, will improve the stratification of patients on adjuvant studies. Further improvements will occur with the advent of gene expression profiling [39].

As several lower dose IFN-α trials show a ‘banana-shaped’ difference between treated and observation RFS curves, a legitimate question concerns the duration of treatment. Several current trials are addressing this question, including the EORTC 18991 trial of slow release pegylated (PEG)-IFN-α2b once a week for 5 years versus observation in patients with resected stage III melanoma.

In an attempt to shorten treatment duration with a more intensive regime, the USA S0008 trial compares 9 weeks of a modified biochemotherapy regime (cisplatin, vinblastine, dacarbazine, IFN-α2b and IL-2) [40] with 1 year of standard HDI.

The E1697 Intergroup trial compares the induction phase alone (1 month of HDI) versus observation in intermediate risk (stage II T3) patients. This is a particularly important study as it is possibly the only remaining trial of HDI with an observation control arm. The early separation of survival curves in the E1684 and E1690 trials, and the failure of HDI trials without the induction component (such as NCCTG 93-7052) further emphasises the importance of this investigation.

The Sunbelt Melanoma Trial investigates the use of standard HDI versus observation in patients with isolated regional lymph node metastases after lymphadenectomy, and observation versus lymphadenectomy alone versus lymphadenectomy plus 1-month of induction HDI in patients with polymerase chain reaction (PCR)-positive isolated regional sentinel lymph nodes.

**Conclusions**

Until agents of improved efficacy and reduced toxicity are available, all patients with intermediate- and high-risk resected melanoma should be entered on randomised clinical trials whenever possible. The use of observation control arms in these studies continues to be justifiable and ethical, but patients with high-risk disease deserve a full explanation of HDI treatment, including the current controversy regarding the interpretation of OS data. They should be told that there is widespread agreement that it prolongs relapse-free 5-year survival by $\sim 10\%$ at the expense of 12 months of treatment involving considerable toxicity, and that the impact on RFS can only reasonably be expected when this drug is administered according to strict guidelines by experienced physicians.

The further refinement of risk groups based on the use of molecular genetic factors, particularly gene expression profiles, promises significant improvement in the sophistication of trial design and outcome.

**References**
