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Adjuvant Treatment of Melanoma

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1. Introduction

Melanomas occur in 95% of cases as skin cancer (1.5-7% of all skin cancers) and only 5% in non-skin locations, especially the eye. The incidence has doubled every 10-20 years since the mid 20th century, but the mortality has not increased in the same proportion. Mortality has increased at a slower rate, thus showing that the higher incidence is mainly at the expenses of early lesions leading to early diagnosis and the application of curative surgical treatment. Globocan's data from 2008 shows an incidence of 199.627 cases and a mortality of 46.372 (M: 101.807/25.860 y W: 97.820/20512), when in 2002 the incidente was 160.000 (M:F sex ratio, 0.97) and the mortality 41.000 (M:F sex ratio, 1.2) The majority of melanomas originate in existing nevi, only 30% are new lesions. Radial or spreading growth initially appears (malignant lentingo melanoma, superficial acral lentiginous melanoma) followed by vertical growth that involves lymphatic colonisation. Nodular melanoma only presents vertical growth, without any previous radial growth phase and this is why it has a worse prognosis. The Clark levels of invasion (I, II, III, IV and V) and Breslow's tumour thickness measurements (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0 mm), are based on the growth depth of histopathological studies and enable evaluating the prognosis and estimating the risk after surgery of the primary tumour (Dyson et al.2005). They indicate the risk of metastasis and are the bases and foundations of studies of tumour extension and classification.

One important step is the study of the sentinel lymph node, which enables precise classification of lymph node affectations. This has good prognosis value and influences making later therapeutic decisions such as the use of high dose adjuvant interferon. Furthermore, in cases where these nodes are positive, it indicates the advantages of early lymphadenectomy. Its indication is for stages I-II of the AJCC, which is without evidence of regional or distant lymph node metastases that may include ultrasonography (Saiag et al. 2005). The Breslow degree of millimetric invasion informs about the risk of hidden metastasis at a lymph node and distal level. If this degree of invasion is less than 1 mm, the positivity of the sentinel lymph node is only 0-5% and the cure rates by surgery are 98%. This means that in this group the indication of performing the sentinel lymph node technique is not logical because of its low indicative value. In patients with a degree of invasion between 1 and 4 mm (T2, T3) the positivity ranges from 1 to 14% in T2 and from 11 to 34% in T3. This is why the sentinel lymph node technique would be very important in this group because of its prognostic and therapeutic repercussions.

In patients with a degree of invasion of more than 4 mm (T4), the risk of regional micro-metastasis is very high, between 20-65%, as is that of distant micro-metastasis (>60%). This means that the sentinel lymph node technique would be less informative regarding palliative lymphadenectomy and the indication of treatment with high dose interferon. This procedure would be indicated from the outset, as the patients are high risk. Nevertheless, it would enable to adequate classification and this would be valuable when planning future clinical trials with more homogeneous groups of patients. (Table 1) (Moreno-Nogueira 2008).

1.- Tumour thickness of more than 1 mm.
2.- Clark level higher than III.
3.- Ulceration.
4.- Histological signs of regression.

Table 1. Histological criteria indicating the sentinel lymph node

A histopathological study of the primary lesion and complementary examinations are the basis of the stage classification as a step prior to planning therapy following surgery. The AJCC/UICC classification of 2001 has evident differences compared to that of 1997. It simplifies the Breslow scale to 1, 2 and 4 mm and consider the presence of ulceration. It adequately classifies lymph node affectation and, in the metastatic phase, distinguishes types of metastasis and the prognosis value of high LDH levels. This disease classification finally includes assessment of the sentinel lymph node. All this enables identification of the different stages as well as different risk groups, an important aspect for deciding complementary treatments (Balch et al. 2001).

Patients with stages I and II have no distant lymph node metastases and survival rates of 40% to 95%, as defined by the degree of infiltration and the presence or not of ulceration. This means that sub-stage IIA is only considered of intermediate risk when it is ulcerated (Breslow 1.1-2 mm) or has a thickness of 2.1-4 mm without ulceration. High risk patients include sub-stage IIB (Breslow 2.1-4 mm ulcerated or > 4 mm non-ulcerated) and IIC (Breslow > 4 mm ulcerated). The variability of survival in these stages indicates its heterogeneity, and so other prognostic factors (mitotic rate, serum YKL-40, PTEN and Ki67 expression, etc.) must be included to better discriminate different patient sub-groups (Liu et al. 2006, Schmidt et al. 2006, Mikhain et al. 2005, Gimotty et al. 2005). Stage III patients are also a very heterogeneous group, with high risk and worse prognosis as they always involve lymph node affectation where the number of affected nodes are an indicator of survival, age, location, and the presence of macro or micro metastasis in the lymphatic nodes (67% vs. 43% up to 5 years, p<0.001) etc. also having an influence. (Tables 2 and 3) (Coit et al. 2006, 11. Balch et al. 2010).

In this stage and in the near future, other factors must be considered such as serum a protein S-100B level which is an independent prognostic factor as an initial baseline measurement but also during the follow up, different gene expressions, circulating melanoma cells, etc. They would provide information in addition to standard clinical and histological information, and bring about an improvement in the precision of both, the diagnosis and the prognosis. It will contribute, as already mentioned, to this therapeutic future (Suciu et al. 2007, Mocellin et al. 2006, Fecher et al. 2007, Tarhini et al. 2009).

Factor	Value of "p"
Patient age	<0.0001
Male vs. female	0.12
Primary location	0.002
Ulceration of primary tumour	0.13
Breslow thickness	0.05
No. of positive nodes	<0.0001
Clinical affectation of nodes	0.0003
Micro vs. macro metástasis in the lymphatic nodes	<0.001
Extranodal extension	0.07

Table 2. Prognostic factors in stage III

Low risk melanomas:
          -Stage I.
 	
Intermediate risk melanomas:
          -Stage II A   (Breslow of 1.1- 2 mm Ulcerated)
                                   (Breslow of 2.1- 4 mm Non-ulcerated).
 	
High risk melanomas:
          -Stage IIB.   (Breslow of 2.1- 4 mm Ulcerated)
                                   (Breslow >4 mm Non-ulcerated)
 	
          -Stage IIC.   (Breslow >4 mm Ulcerated).
          -Stage III.

Table 3. Melanomas: risk groups

2. Adjuvant treatment

The treatment of choice for localised primary cutaneous melanoma (stages I, II and III) is surgery and if there is regional affectation of the lymph nodes or if the sentinel lymph node is positive, this must be completed with lymphadenectomy. The resection should be deep in accordance to the thickness of the primary lesion. The recommended width of the margins should be 1 cm, for lesions 1 mm thick. In melanomas of 1-4 mm, about 2 cm is recommended and for lesions of more than 4 mm, about 3 cm. Elective regional lymphadenectomy is not recommended unless the study of the sentinel lymph node was positive. Up to 37% of these cases have nodes affected. Therapeutic lymphadenectomy should be performed when lymph nodes metastases have been clinically diagnosed. Surgery should be assessed once again for the metastatic disease, especially for metastases of the skin or those attached to organs, and they would be considering as candidates for adjuvant treatment.

The rationale of adjuvant treatment to surgery is based on the poor prognosis of high-risk melanomas, with a relapse rate of 50-80% and a low five-year survival of 25-70% (Moreno-Nogueira, 2008). Another reason would be that metastatic disease has no efficient treatment capable of significantly prolonging patient survival.

Patients included in the high-risk group should be assessed for adjuvant treatment with high doses of Interferon-α2b, as it is the only treatment shown to significantly improve disease free and possibly global survival.

Different types of adjuvant treatment have been investigated and others are under study and pending results.

2.1 Adjuvant treatment with chemotherapy

In randomised studies, adjuvant chemotherapy has not shown any significant benefits, even at high doses with the support of autologous bone marrow. (Table 4) (Moschos and Kirkwood, 2005).

Authors	No. of cases	Stage	Treatment	Follow-up (years)	Statistical significance
Fisher 1981	181	II-III	CCNU Observation	3 y.	NS
Veronesi 1982	931	II-III	DTIC BCG DTIC+BCG Observation	5 y.	NS
Lejeune 1988	325	I-IIA-IIB	DTIC Levamisole Placebo	4 y.	NS
Meisenberg 1993	39	III	Autologous bone marrow transplant	N.A.	NS

NA: Not announced. NS: Not significant.

Table 4. Melanomas: Adjuvant chemotherapy. Randomised studies

2.2 Adjuvant treatment with biochemotherapy

Various studies, with contradictory results, have been published of combined treatment with chemotherapy and cytokines; nevertheless, this is an interesting line for further investigation. A first study with 138 patients, 71 treated with biochemotherapy (cisplatin + vinblastine + DTIC + IFN + IL2) compared to two treatments with high dose Interferon-α2b, (33 patients.) vs. intermediate doses (33 patients.), did not show any significant differences in the groups regarding GS and RFS (Kin et al. 2006). A second study compared two cycles of DTIC 850 mg/m2 followed by Interferon-α2b 3 mill./3 s.c., during six months, compared to observation in patients with stage IIa, IIb, IIIa and IIIb. There were no significant differences regarding RFS and GS in low risk patients (IIa), but the differences were significant in high risk patients with a RFS at 5 years of 42% vs. 17% (p=0.0018) and a GS at 7 years of 51% vs. 30% (p=0.0077). The benefits were more evident in metastasis free survival and the procedure has an acceptable toxicity (Stadler and Luger, 2005). On the other hand, a wide Phase III study from DeCOG (*Dermatologic Cooperative Oncology Group)* with 441

patients with regional lymphatic clearance after having positive nodes compared: IFN α2a, 3 MU s.c. three times a week (A), (A) plus DTIC 850 mg/m2 every 4-8 weeks for two years (B) and just observation (C). The results showed significant improvement in RFS and OS in group A vs. C, but with no differences between B and C, meaning possibly that DTIC reverts the benefits of adjuvant IFN (Garbe el al. 2008).

There are also some studies of neoadjuvant treatment with biochemotherapy. One in Stage III with 48 patients analysed the association of cisplatin + vinblastine + DTIC + IFL + IL2. At five years the GS was 66% and the RFS was 56%, higher than historic controls (Lewis, 2006).

2.3 Adjuvant treatment with immunostimulants

Seven studies with non-specific immunostimulants did not show any significant benefits (Table 5) (Moschos and Kirkwood. 2005)

Authors	No. of cases	Stage	Treatment.	Follow-up (years).	Statistical significance
Balch 1982	260	III	C. parvum	2 y.	NS
Paterson 1984	199	I-II	BCG	4 y.	NS
Miller 1988	168	II-III	Transfer factor Observation	2 y.	NS
Lipton 1991	262		C. parvum BCG	4 – 9 y.	CS
Quirt 1991	577	I-IIA-IIB-	Levamisole BCG BCG+Levamisole Observation		
Spitler 1991	216	I-IIA-IIB-III-IV	Levamisole Observation	10 y.	NS
Czarnetzki 1993	353	ii	BCG (RIV) BCG (Pasteur) Observation	6 y.	NS

CS: Close to significance. NS: Not significant.

Table 5. Melanomas. Adjuvant treatment with non-specific immune stimulants. Randomised studies

2.4 Adjuvant treatment with vaccines

Various vaccines against melanoma are currently under development, some of them in Phase I, II and III clinical trials, but in general they have not offered any advantages except in one study which only included 38 patients (Table 6) (Moschos and Kirkwood, 2005).

Melacine, a vaccination made from cell lysate was compared to observation by SWOG (*Southwest Oncology Group*) in patients with melanoma of 1.5-4 mm in thickness without lymph node affectation. No benefit was observed but a retrospective analysis showed that the vaccinated patients that had positive HLA-A2 or C3 presented a disease free survival of 77% compared to 64% of patients with the negative marker observed (Sosman et al. 2002). In the ECOG 1694 study, the group that received the vaccination of Ganglioside GM2 activator protein fared worse than the group with high doses of Interferon-α2b after a relatively short

Authors	No. of cases	Stage	Treatment	Follow-up (years.)	Statistical significance
Livingston 1994	123	III	GM2+BCG+CFM BCG+CFM	5 y.	NS
Wallack 1995	250	II	Virus allogeneic polyvalent melanoma cell lysate	2.5 y.	NS
Wallack 1998	250	III	Melanoma cell lysate vaccine	3 y.	NS
Bystryn 2001	38	III	Polyvalent shed antigen Placebo	2.5 y.	S
Sondak 2002	689	IIA	Melacine and DETOX Observation	5.6 y.	NS
Hershey	700	IIB	Cell lysate vaccine Placebo	8 y.	Tendency in RFS/GS

Table 6. Melanomas. Adjuvant treatment with vaccines. Randomised studies

	RFS		DMFS		OS	
	OBS	GM2-KLH/QS-21	OBS	GM2-KLH/QS-21	OBS	GM2-KLH/QS-21
N° events	204	205	143	52	112	124
4-yr %(SE%)	69.4% (1.9%)	68.2%(1.9%)	78.8%(1.7%)	6.1%(1.8%)	83.6%(1.6%)	81.5%(1.6%)
HR (95% CI)*	1.03 (0.84, 1.25)		1.11 (0.88, 1.40)		1.16 (0.90, 1.51)	
P value*	0.81		0.36		0.26	
Abbreviation: HR, hazard ratio. * Cox model, stratified for stratification factors. OBS: Observation. RFS: Relapse-free survival. DMFS: Distant metastasis-free survival. OS: Overall survival						

Table 7. Final results of study EORTC 18961

median follow-up. However this study did not include a control group without adjuvant treatment, and so it is not possible to determine whether vaccination with ganglioside was equivalent to observation or even prejudicial (Kirkwood et al., 2001). A recently presented randomised trial, where 604 patients in stage III were enrolled between April 1997 and January 2003, studied vaccination of allogeneic melanoma lysates with low doses of Interferon α-2b, compared to high doses of Interferon α-2b. At five years there were no differences in GS (61% vs. 57%) or RFS (50% vs. 48%), between both groups, but these figures were better than those for patients who did not receive any adjuvant treatment. The incidence of important side effects was similar, but the neuropsychiatric toxicity was higher in the second group (Mitchell et al., 2007). The final results of the Phase III Study form EORTC 18961 have been presented in the ASCO 2010 meeting. The study had 1314 patients

in stage II (T3-T4N0M0), between March 2002 and December 2005, divided into two groups, the ones with GM2-KLH/QS-21 vaccination after surgery and the ones that were just observed. The study had to be stopped because it did not show good results as supposed and the vaccination could be potentially harmful to patients. (Table 7) (Eggermont et al, 2010).

2.5 Adjuvant treatment with interferon

At present the most common adjuvant treatment in high risk melanomas is Interferon-α2b at high doses according to the Kirkwood scheme (Induction: Interferon-α2b: 20 million/m2, i.v., 5 days a week for four weeks. Maintenance: Interferon-α2b: 10 million/m2, s.c., three times a week for 48 weeks), which should also be assessed after metastasis surgery, without evidence of tumour.

Interferon is a glycoprotein described in 1957 by A. Isaacs and J. Lindemann as a product of virus infected cells that interfered with the replication of live virus in cell cultures. In the eighties, cloning by genetic engineering of a human interferon gene in *Escherichia coli*, enabled the production of large amounts of interferon thus simplifying clinical research into cancer treatments. There are more than 20 varieties, but the three most important are Interferon α, β, and γ, all being used in clinical oncology, especially α.

The genes that code interferon α and β are found in chromosome 9, whereas the gene coding the γ is in chromosome 12. Both α and β are structurally similar, with the same number of amino acids, the homology of the sequence of nucleotides being 45% and 29% for amino acids.

Interferon acts by binding to a specific membrane receptor protein, thus unleashing a cascade of signals whose end result is the expression of a certain number of genes. Interferon α and β share the same receptor, but β has greater affinity. The gene of this receptor has been found in chromosome 21 and for interferon γ in chromosome 6 (Faltynek et al. 1986, Pestka, 1997).

The proteins produced as a result of gene activation and expression, participate in different biological activities such as antiviral and immunomodulating actions, reduction of cell proliferation, suppression of gene expressions, inhibition of angiogenesis, induction of cell differentiation etc.

Oncological pathology essentially uses Interferon α (IFNα-2a and IFNα-2b) as a single agent or in combination with chemotherapy or other cytokines and monoclonal antibodies. Interferon-α2b was the first to be produced using the DNA recombinant technique and approved by the United States FDA. Over the last 15 years numerous studies have been carried out in various neoplasias, including lymphomas, CML, melanomas and kidney cancer.

The antineoplastic activity of interferon has a double mechanism, it inhibits the proliferation and growth of tumour cells, directly affecting all phases of the cell cycle (M, G1 and G2), prolonging the cell cycle and reducing the number of cells that enter phase S and G2. The accumulative effect of prolongation of the cell cycle has cytostatic action and increases apoptosis. In second place it acts indirectly by inducing an increase of the antigen expression of the Class I and II major histocompatibility complex on the surface of tumour cells, exercising an effect on modulation of the immune response to these cells. These antigens play an important role in recognition of neoplastic cells by cytotoxic T-cells together with increasing the effectiveness of all effector immune cells with cytotoxic capacity

(NK cells, macrophages etc.) on these tumour cells. The increased interferon induced expression of TNF-α receptors on the surface of these cells, and increases the cytostatic and cytotoxic action of TNF-α, whose production is also increased. Something similar also occurs with other cytokines (CSF, IL1 etc.) that are involved in immune antitumorigenic cytotoxicity mechanisms (Foss, 2002).

Another effect of interferon is the inhibition of tumour angiogenesis. Systemic treatment with interferon α and β reduces growth endothelial cells, essential for the formation of new vessels, by inhibition of angiogenic factors, thus having an indirect anti-proliferation effect. Interferon α reduces the expression of FGF-2 and the transcription of VEGF. This is further enhanced by another possible mechanism, inhibition of IL-8, which has neo-angiogenic capacity in numerous neoplasias.

Interferon has been widely investigated in melanomas, both as adjuvant to locoregional treatment, as well as in the metastatic phase in the case of a tumour with evident immunogenic activity.

The adjuvant treatment most recognised at present in high-risk melanomas specially in USA is Interferon-α2b at high doses and according to the Kirkwood scheme. This scheme has been used by the *Eastern Cooperative Oncology Group and Intergroup* to perform four randomised studies on 1916 patients whose data was updated in 2004 (Figure 1).
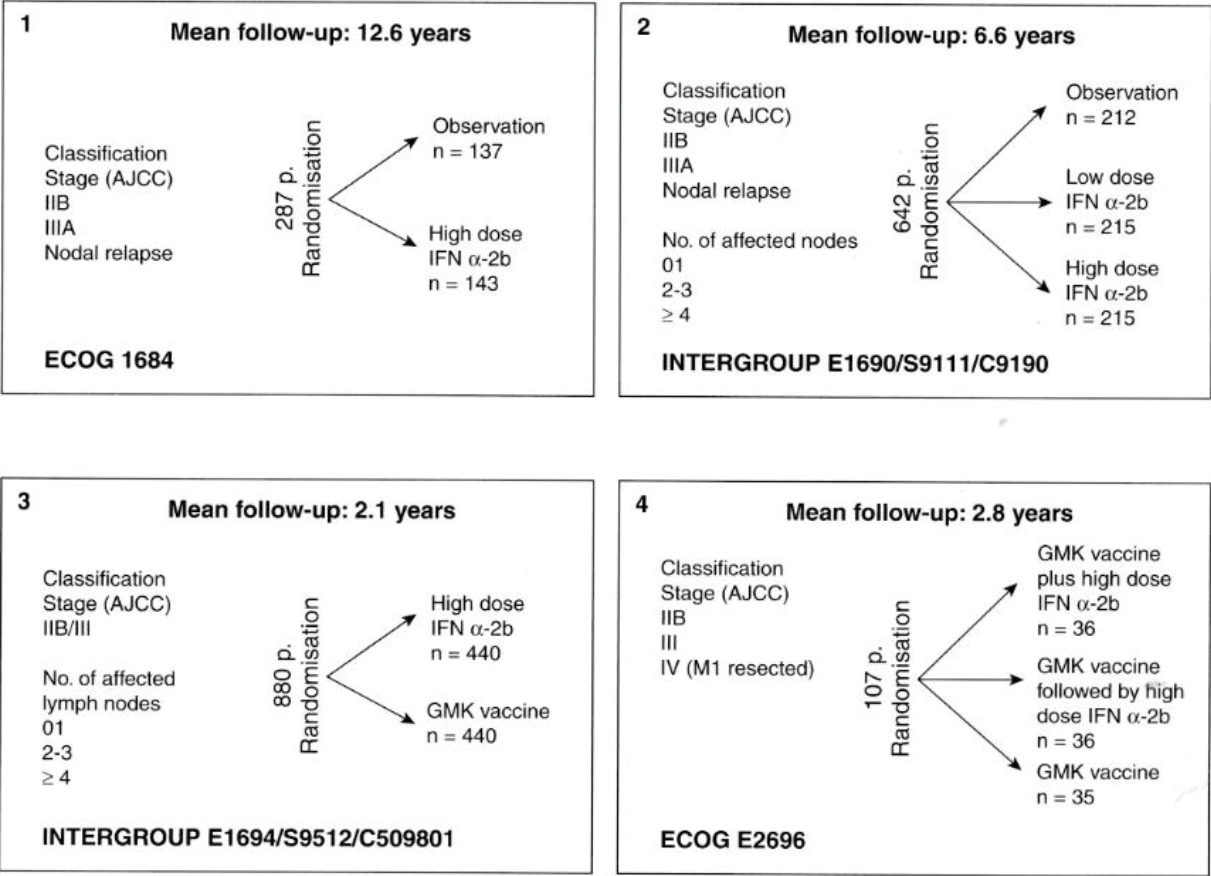

Fig. 1. Eastern Cooperative Oncology Group and Intergroup IFN

The first study, E1684, showed that patients who received adjuvant treatment presented a recurrence free survival (RFS) at five years of 37% compared to 26% (p=0.0023) in the

untreated group. The global survival at five years was also significantly better (46% vs. 37%, p=0.0237) and this information enabled approval of IFN-α 2b as adjuvant treatment in high risk melanomas by the United States FDA, as well as the Spanish Ministry of Health.

When this study was updated with a median follow-up of 12.6 years, it maintained the benefits in RFS (HR=1.38, p=0.02). The benefits for GS descended slightly (HR=1.22, p=0.18), but this could be due to deaths by other causes in the elderly population of the study (current mean age of > 60 years).

The second E1690 study also showed benefits in RFS after a follow-up of 6.6 years (HR= 1.24; p2=0.09), but not for GS.

In the combined analysis of these two ECOG studies with 713 patients and a median follow-up of 7.2 years, high doses of Interferon-α2b were better than the observation group in regard to the RFS (HR= 1.30, p < 0.002). However this analysis showed no benefit in global survival (GS) (HR= 1.08, p=0.42). (Figure 2).
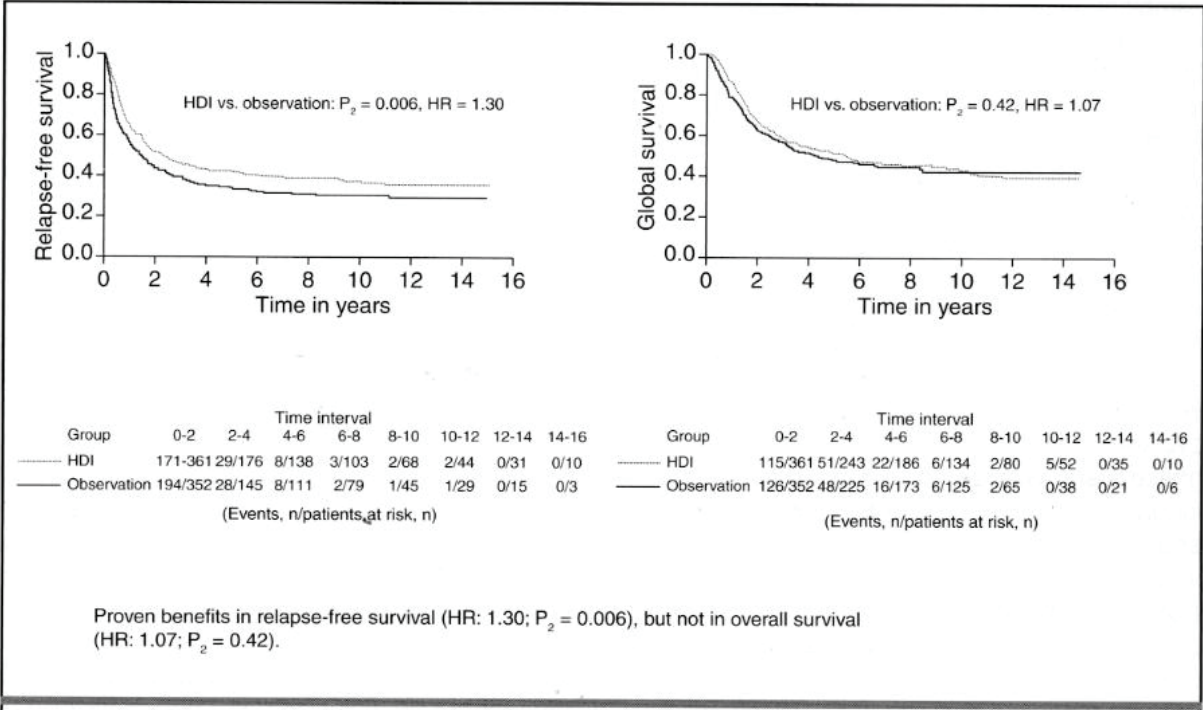

Fig. 2. Joint analysis of the E1683 and E1690 studies recurrence free survival/global survival

Study E1694 showed benefits in RFS and GS compared to GMK vaccine after a median follow-up of 2.1 years. Equally, study E2696 showed that the combination of GMK vaccine and Interferon-α2b at high doses reduced the risk of relapse compared to GMK alone (Figure 3) (Kirkwood et al. 2004).

In view of the above, it is possible to say that in patients with resected high risk melanoma Interferon-α2b at high doses is an adjuvant treatment with clear evidence of increased RFS and moderate, but not significant, improvement of GS. Toxicity should be well assessed and explained to each patient, so that he/she participates in the decision making process. Adequate experience in the use of high dose interferon, with control of its toxicity and recommending good hydration, means that the majority of patients comply with the therapeutic plan and a relatively low number of dropouts. The most outstanding toxicity reactions are asthenia, neuropsychiatric symptoms, myelosuppression, alteration of liver

enzymes, etc. The neuropsychiatric effects may appear early or tardive and include signs of depression, anxiety and occasionally suicidal thoughts. (Table 8)
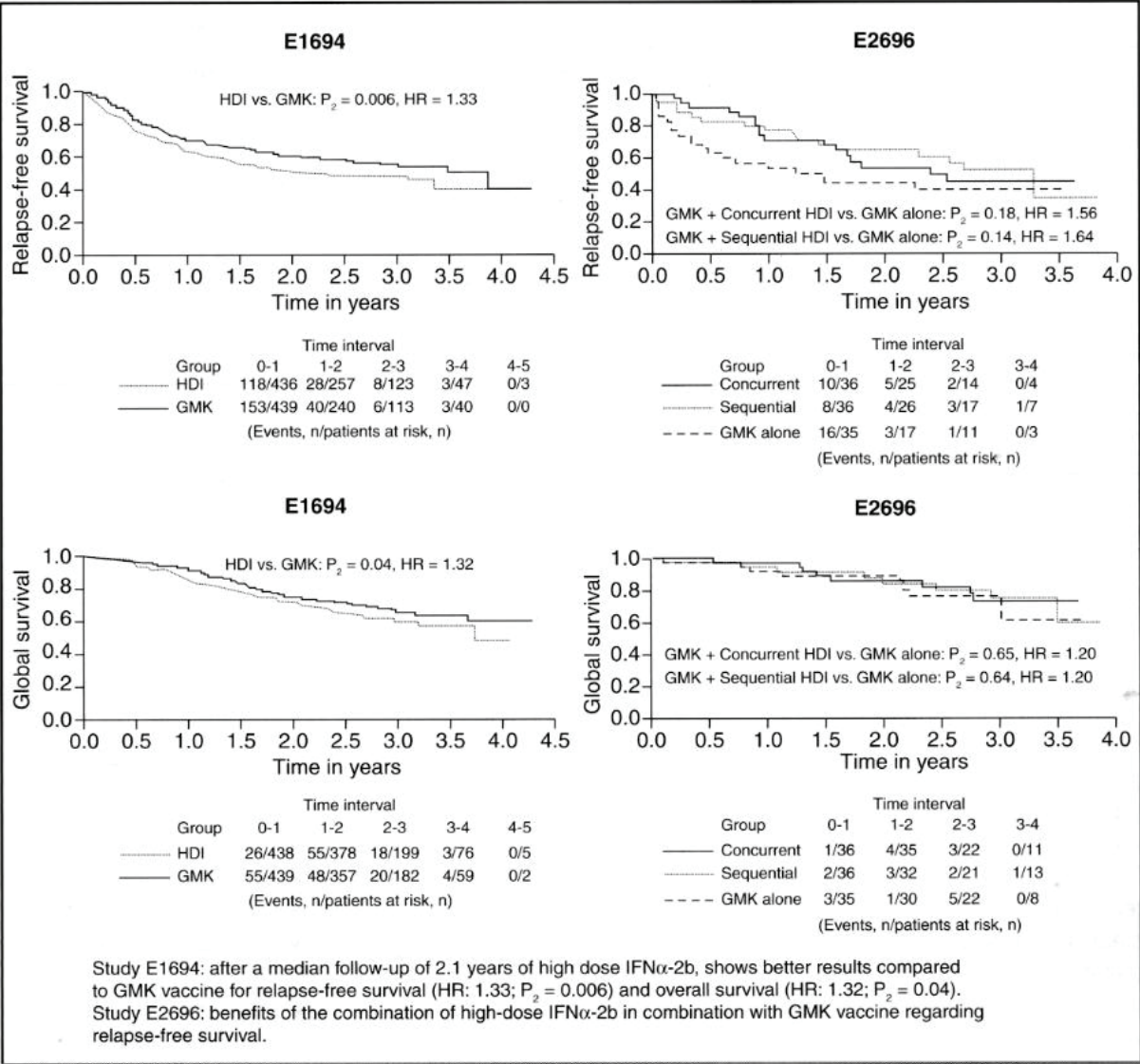

Fig. 3. Studies E1694 and E2696. Recurrence free survival/global survival

In conclusion, there are arguments in favour of the use of high dose Interferon-α2b as this treatment shows improvement of disease free survival in all studies carried out to date, and increased, but not statistically significant, global survival. The toxicity is undoubtedly high, but manageable in services with experience. Furthermore, there is no other therapeutic regimen that has shown benefits in adjuvant treatment of melanoma. However, there are also arguments against high dose Interferon-α2b. In the first place it is not clear which patient population really benefits from adjuvant treatment. The only clear benefit is for disease free survival; no consistent data is available for global survival. In second place the toxicity is considerable and requires a team with experience in its management even though a certain number of patients will abandon or suspend treatment for this reason. Finally the duration and ideal dosage for the treatment is unknown. (Table 9) (Jonasch and Haluska. 2001, Trask et al. 2000).

	Patients (%) *	Patients (%) *
Adverse effects	All degrees	Degree 3-4
Asthenia	96	21-24
Fever	81	18
Myalgia	754	4-17
Nauseas	66	5-9
Vomiting	66	5
Myelosuppression	92	26-60
Elevated AST	63	14-29
Neuropsychiatric symptoms	40	2-10
- Depression. - Anxiety - Suicidal thoughts	0-70%	
* Data taken from the E1684 study of 143 patients. ** Data taken from the E1684, E1690 and E1694 studies.		

Table 8. Most common adverse events (degree III/IV) in patients treated with high dose IFN-α2b

1) ARGUMENTS IN FAVOUR.
• A consistent improvement in disease free survival has been demonstrated • in all studies carried out. • An improvement in global survival has been shown, but without this being statistically significant. • The toxicity is high, but manageable by experienced medical teams. • No other therapeutic regime has shown benefits in the adjuvance of melanoma.
2) ARGUMENTS AGAINST.
• It is not clear which population most benefits from the adjuvant treatment. • The benefit is only clear for disease free survival, there being no consistent information referring to global survival. • The toxicity is considerable. • The ideal duration and dose for the treatment are unknown

Table 9. Arguments for and against high dose interferon as adjuvant treatment

Other favourable arguments are the data from a study that analysed the quality adjusted survival (QAS) using clinical data from the E1684 and E1690 studies which pointed out that the majority of patients showed improvement of the QAS, but the benefit was only significant in 16% of patients in the E1684 study (Kilbridge et al. 2002).

A cost-effectiveness analysis of high dose Interferon-α2b as adjuvant treatment for high-risk melanomas in Spain, shows that it is within established limits for healthcare economy regarding the use of a new treatment (Gonzalez-Larriba et al. 2002). Another recent study of cost effectiveness in node positive melanomas shows, that the treatment was cost effective, even though it varied according to the sub-stage, and also highly effective in terms of quality of life per year in patients under 60 years of age with stage IIIC melanoma (Cormier et al. 2007).

Even more recently a Stage III study was published comparing i.v. induction of Interferon α2b to the classic high dose scheme with induction and maintenance. At 51 months of follow-up, the RFS was 32 months vs. 31 months (p=0.836) and the GS was 61 months vs. 63 months (p=0.444), without being significant differences. There were more dropouts in the classic treatment (p<0.001), mainly because of its duration and signs of recurrence more than for toxicity. This study, which included 355 patients, attempted to show the value of induction (no differences between both groups), but lacked on untreated control group, could not confirm this in a more evident way. However, the existence of this group was not considered after the information published on the benefits of adjuvance (Gogas et al. 2007).

Another similar study presented in ASCO 2010 showed that patients in stage IIB and IIIA have similar RFS and OS in both groups, the ones with induction plus 8 weeks of maintenance dose and the ones with high doses according to Kirkwood regime (Sullivan et al. 2010). In high risk melanomas there is another study in Phase III with 364 patients that compares 4 weeks of induction versus 1 year of treatment with classic high doses of IFN, showing no significant differences in RFS and OS between both regimens (Pectasides et al. 2009). There is also another Phase III randomized study from DeCIG MM-ADJ-5 with 380 patients in stage III that compares 3 treatments with IFN α2b 20 MU/m2 i.v, five days a week for four weeks every four months and the classic regimen of high doses of IFN from Kirkwook, showing no significant differences in DMFS, but with better tolerance and safety with the intermitent treatment (Mohr et al. 2008). Therefore shorter regimens might encourage the use of IFN as an adjuvant treatment in melanoma patients.

As a final summary it can be said that in patients with high risk resected melanoma, high dose interferon is the adjuvant treatment to be proposed, together with background information on its collateral effects, as there is clear and significant evidence of improvement in the RFS and moderate, although not significant improvement of the GS.

New data have recently been published on high dose Interferon-α2b according to the Kirkwood scheme as neoadjuvant treatment prior to lymphadenectomy, in patients with palpable stage IIIB and IIIC adenopathies. After four weeks of intravenous phase among the 20 patients enrolled, 11 (55%) showed response, three of them (15%) pathological complete response. At a median of 18.5 months follow-up, 10 patients continued disease free. In responding patients, cells CD11+ and CD3+ increased on the tumour and CD83+ decreased, indicating a correlation between reactivity of the immune system and the benefit of the treatment. This study also included molecular analysis with activation of STAT3 being observed and related to cell proliferation, high dose Interferon-α2b would reduce this protein and increase STAT1. This enables opening a new approach to adjuvant treatment in high risk patients which should be more widely explored (Moschos et al. 2006).

Low and intermediate doses have not shown any real benefits in the adjuvant treatment of high-risk melanomas (Table 10) (Eggermont et al. 2005).

Trial	No. of cases	SLE	OS
Low dose IFN (3 mU x 3/s x 3 y.):			
-WHO-16 (2001)	426	NS	NS
-UK (2004)	674	NS	NS
-Scottish study (2001)	59	NS	NS
Ultra-low dose IFN (1 mU):			
-EORTC/DKG-80 (2001)	830	NS	NS
Low dose INF + Isotretinoin (IFN: 3 mU x 3/s x 2 y.)			
-ECAMTSG (2005)	407	NS	NS
Intermediate dose IFN.			
-EORTC 18952	1388	NS	NS
(10 mill. 13 m vs 5 mill. 25 m. vs observation)			

Table 10. High risk melanomas: adjuvant treatment with low and intermediate dose interferon

But in the review by A. Verma et al. (2007),patients with high risk melanomas, the results show, that treatment with high doses of IFN constantly improve the SLR and the mortality rate at two years (p<0.03). The authors conclusion is that IFN at high doses is a reasonable option in selected patients. A recent meta-analysis evaluating 6067 patients from 10 trials found significant benefits in RFS and GS (p=0.00006 and p=0.008), even though the absolute benefits on survival are small, just a 3% at five years. This meta-analysis did not clarify the ideal dose of interferon neither the duration of the treatment and found a sub-group where the benefits were greater, the presence of ulceration in the primary tumour, but this needs clarification. (Wheatley et al. 2007).

A recent Phase III randomized study from DeCOG, has compared low doses of IFN α2b (3MU three times a week) for 18 months (group A) versus 60 months (group B), in patients with primary melanoma, a Breslow's thickness ≥ 1.5 mm and negative lymphadenopathies clinically. The 75.6% of them had a sentinel lymph node biopsy, with a positive results in 18% in the group A and 17.5% in the group B. Overall they had 840 patients, with a median follow up of 4.3 years, and it did not show any benefits with prolonged treatments. All this suggest that the optimal length of the treatment with IFN is still nuclear (Hauschild et al. 2010).

It has been published recently some data on adjuvant treatment with pegylated Interferon α2b (PEG-IFN) from the EORTC 18991 study (Induction of 6 µg/Kg/week, s.c. for 8 weeks, followed by maintenance at the dose of 3 µg/Kg/week, s.c., for a total duration of 5 years). The study included 1256 patients in stage III (any T, N1-2, Mo, without metastasis in transit). Patients were randomised into two groups, one for treatment (608 p.) and the other for observation as a control (613 p.). The randomization was divided into positive microscopic lymphadenopathy (N1) versus macroscopic one (N2), number of positive lymph nodes, tumour ulceration and Breslow's thickness, sex of the patients and the referral center, analysing the data according to the intention to treat. The average length of treatment with PEG-IFN was 12 months (IQR: 3.8-33.4). The mean follow up was 3.8 years, and 328 recurrences were observed in the interferon group vs. 368 in the control one (p=0.01), being at four years the RFS value 45.6% in the first group and 38.95 in the second one, showing a risk reduction of 18% (p=0.01). No significant differences were observed between the two groups in OS. Grade 3 adverse event occurred in 246 (40%) patients in the interferon group and 80(10%) in the observation group; grade 4 adverse events occurred in 32 (5%) patients in

interferon group and 14 (2%) in the observation group. In the interferon group the most common grade 3 or 4 adverse events were fatigue (97 patients, 16%), hepatotoxicity (66 patients, 11%), and depression (39 patients, 6%). Treatment with PEG-IFN was discontinued because of toxicity in 191(31%) patients. Regarding the quality of life, there was a negative effect in the group treated with IFN with a decrease in social activity and appetite. Knowing that PEG-IFN increases the RFS, the patients should be informed about the negative effects of the treatment and they should be encourage to participate in the planning of it (Table 11). (Eggermont et al., 2008; Bottomley et al., 2009).
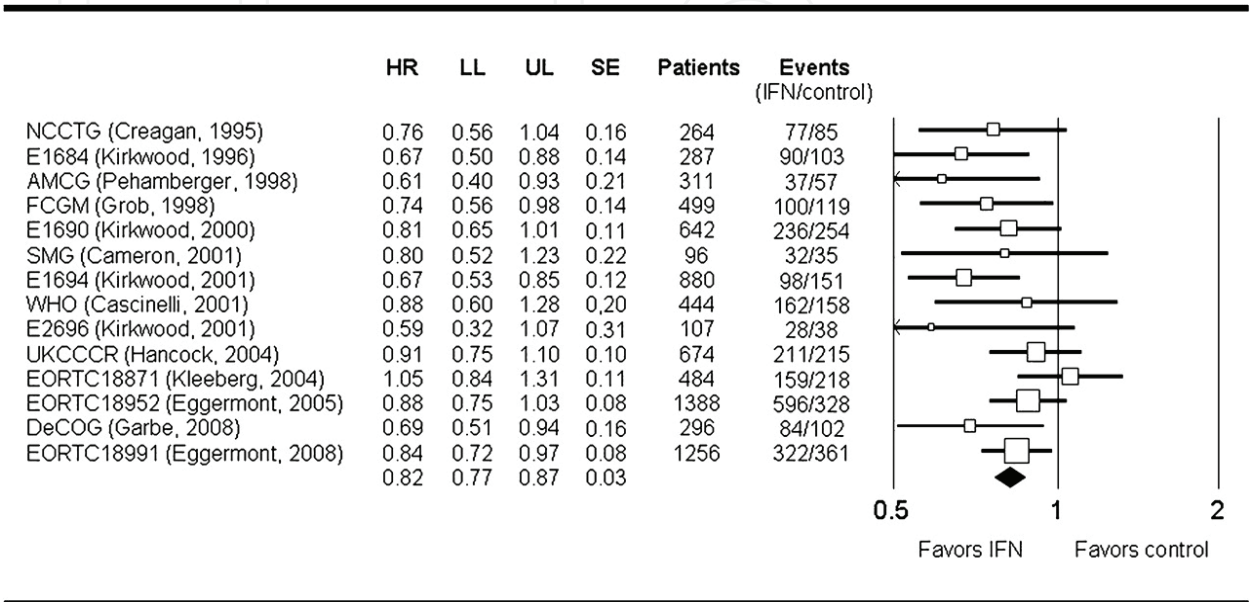
	RFS		DMFS		OS	
	Obs.	PEG-IFN	Obs.	PEG-IFN	Obs.	PEG-IFN
No. of events	368	328	325	304	263	262
Rates at 4 years	39%	46%	45%	48%	56%	57%
Mean years	2.1	2.9	3.0	3.8	NR	NR
HR (95% CI)	0.82 (0.71-0.96)		0.88 (0.75-1.03)		0.98 (0.82-1.16)	
Value of "p"	0.01		0.11		0.78	

Table 11. Pegylated interferon. Results of the EORTC 18991 study

The EADO trial is a Phase III study with excised melanomas ≥ 1.5 mm of thickness and no affected lymph nodes clinically. Patients were randomized to received IFNα-2b (3 MU subcutaneously three times a week for 18 months) versus PEG-IFN (100 mcg. Subcutaneously once a week for 36 months). Out of 898 patients included, 896 were evaluated (453 IFN and 443 PEG) with a mean follow up of 4.7 years. Sentinel node biopsy was performed in 68.2% because it was not a standard procedure initially. The recurrence free survival (RFS) was 64.8% vs. 66.2% (p=0.43), the distant metastasis free survival (DMFS) was 72.6% vs. 71.3% (p=0.55), not showing significant differences. Adverse effects of grade 3-4 were seen in 26.6% vs. 44.6% in the first 18 months, which affected the mead length of treatment (17.8 months vs. 19.2 months, completing the full 36 months of treatment 28% of the patients). In summary, low doses of PEG-IFN was no better than low doses of conventional IFNα-2b. Trying to increase the benefits of PG-IFN by increasing the length of the treatment up to three years is not easy, because the high numbers of patients not completing the full treatment due to the side effects is important and therefore would not solve the clinical needs of them (Grob et al. 2010). Advocating the use of IFN in melanomas, a new meta-analysis has recently been published with a large number of patients reviewing the adjuvant treatment with IFN-α in high risk cases, in relation to DFS and OS, and also it has been studied the effect of the doses and the length of the treatment. There were 14 randomized studies included between 1990 and 2008, with a total of 8122 patients, out of which 4362 were treated only with IFN-α, the rest were only observed. The treatment with IFN-α is associated to and improvement of the DFS (p< 0.001/ 18% risk reduction) and also of the SG (p=0.002/ 11% risk reduction) (Figures 4 and 5).
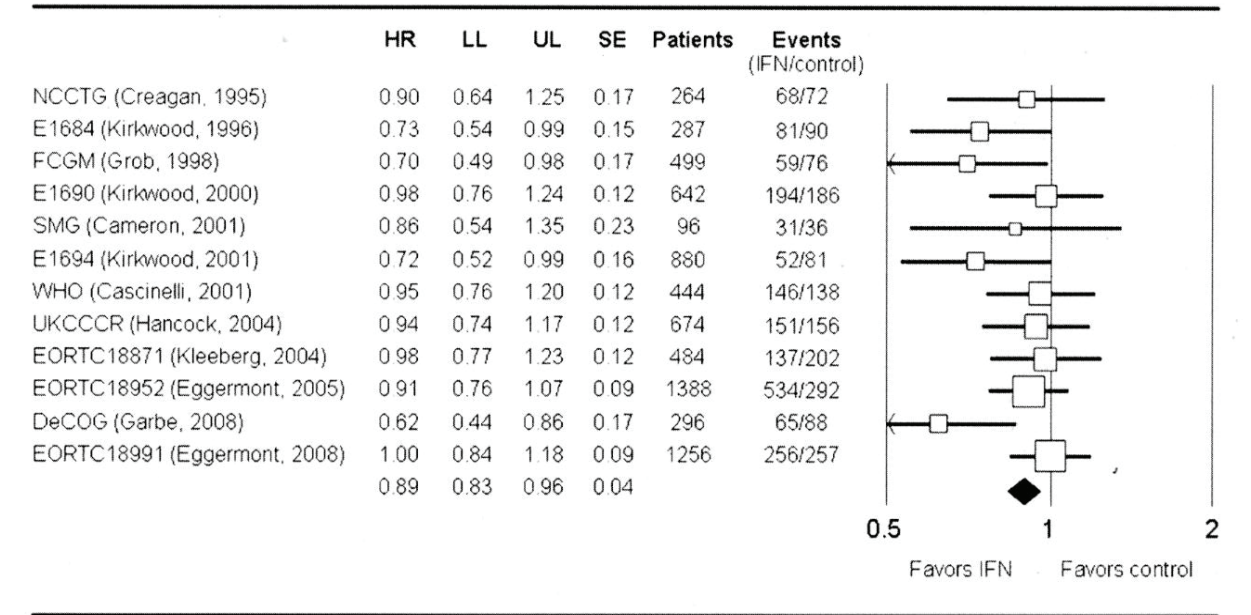
The study has its own limitations according to the authors and therefore it cannot recommend the regime, doses or length of the treatment, neither, which subgroup of patients would respond better the adjuvant therapy. Given the lack of and effective systemic treatment to treat the melanoma, the meta-analysis suggests the use of IFN-α on the daily

clinical bases to offer the patients the best survival opportunities. It is important to remember that other adjuvant therapies well established for other types of cancer like breast, colorectal and ovarian is associated with a risk reduction. These data suggest that it is very important to research the molecular mechanism that could explain the sensibility to the IFN-α to try to identify the group of patients that would benefit most from it (Mocellin et al. 2010).

	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.76	0.56	1.04	0.16	264	77/85
E1684 (Kirkwood, 1996)	0.67	0.50	0.88	0.14	287	90/103
AMCG (Pehamberger, 1998)	0.61	0.40	0.93	0.21	311	37/57
FCGM (Grob, 1998)	0.74	0.56	0.98	0.14	499	100/119
E1690 (Kirkwood, 2000)	0.81	0.65	1.01	0.11	642	236/254
SMG (Cameron, 2001)	0.80	0.52	1.23	0.22	96	32/35
E1694 (Kirkwood, 2001)	0.67	0.53	0.85	0.12	880	98/151
WHO (Cascinelli, 2001)	0.88	0.60	1.28	0,20	444	162/158
E2696 (Kirkwood, 2001)	0.59	0.32	1.07	0.31	107	28/38
UKCCCR (Hancock, 2004)	0.91	0.75	1.10	0.10	674	211/215
EORTC18871 (Kleeberg, 2004)	1.05	0.84	1.31	0.11	484	159/218
EORTC18952 (Eggermont, 2005)	0.88	0.75	1.03	0.08	1388	596/328
DeCOG (Garbe, 2008)	0.69	0.51	0.94	0.16	296	84/102
EORTC18991 (Eggermont, 2008)	0.84	0.72	0.97	0.08	1256	322/361
	0.82	0.77	0.87	0.03		

0.5   1   2

Favors IFN   Favors control

HR: Hazard ratio. LL: Lower limit. UL: Upper limit. SE: Significant estimate.

Fig. 4. Meta-analysis. Disease-free survival

	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
E1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	52/81
WHO (Cascinelli, 2001)	0.95	0.76	1.20	0.12	444	146/138
UKCCCR (Hancock, 2004)	0.94	0.74	1.17	0.12	674	151/156
EORTC18871 (Kleeberg, 2004)	0.98	0.77	1.23	0.12	484	137/202
EORTC18952 (Eggermont, 2005)	0.91	0.76	1.07	0.09	1388	534/292
DeCOG (Garbe, 2008)	0.62	0.44	0.86	0.17	296	65/88
EORTC18991 (Eggermont, 2008)	1.00	0.84	1.18	0.09	1256	256/257
	0.89	0.83	0.96	0.04		

0.5   1   2

Favors IFN   Favors control

HR: Hazard ratio. LL: Lower limit. UL: Upper limit.

Fig. 5. Meta-analysis. Overall survival

Given the characteristics of adjuvant treatment with Interferon-α2b, it would be extremely important to find factors predicting efficiency and parameters for classification of patients to enable a better choice of therapy. Autoimmunity seems to be a factor predicting efficiency in adjuvant treatment with interferon. A prospective study with high dose interferon analysed the autoimmune response through the appearance of thyroid, anticardiolipins, antinuclear, antiDNA autoantibodies or the presence of depigmentation. A quarter of all patients treated develop autoimmunity phenomena. After a follow-up of 45.6 months, only 13% of those presenting autoimmunity had suffered relapse and 4% had died. In the group that presented no autoimmunity reactions, 73% suffered relapse and 54% died. The mean survival has not been reached among the patients with autoimmunity phenomena and was 37.6 months in the group without these manifestations. Therefore, after multivariate analysis, autoimmunity constitutes a significant predictive factor for global and disease free survival (Gogas et al. 2006).

On the other hand, the trial 18991 from EORTC where adjuvant IFN was compared versus control, the presence or not of autoantibodies (anti-cardiolipin, anti-thyreoglobulin y antinuclear) did not represent an important prognostic factor and did not find a significant relationship with the treatment (Bouwhuis et al. 2010).

The determination of HLA is also a factor predicting recurrence in patients treated with Interferon α2b as adjuvant treatment. The percentage of relapse is significantly lower in patients with HLA genotype A33, HLA B57, HLA-Cw03 and HLA-Cw06. (Gogas et al. 2006).

It therefore seems essential to be able to discriminate those patients who would really benefit from adjuvant treatment with Interferon α2b, thus avoiding all side effects in patients that would not really benefit. In addition, this would also have a considerable economic impact.

2.6 Adjuvant treatment with GM-CSF

The GM-CSF is an important hematopoyetic growth factor, codified by a gene placed in the long arm of chromosome 5 (5q21-q32), present in monocytes, fibroblasts and endothelial cells, with an stimulating action over the developing and maturation of stem cells that will become neutrophils, eosinophils monocytes and macrophages. Is has been use therapeutically to treat QT induced neutopenias. The in-vivo studies have shown that recombinant GM-CSF increases the citotoxic activity of monocytes and lymphocytes, and also increases the activity of macrophages by increasing the production of matrix metaloprotheasas and angiogenesis inhibitors, and therefore an overall anti-tumoral effect, together with the increased inmunogenicicy of the tumoral cell, facilitating the antigen presentation. The reason for its use as an adjuvant therapy in excised high risk melanoma is because it also induces dentritic cell differentiation. In 2000 the first results were published on GM-CSF showing benefits on survival in relation to historic controls in stage III patients with a poor prognosis or stage IV with resected disease. Recent data on 98, high risk patients under treatment for three years, show a mean survival of 58.7 months, longer than the result of 37.5 months obtained in the first study where treatment only lasted one year. The benefits were especially observed in stage IIIc. The conclusion was the superiority of long-term treatment over three years, especially in patients that maintained eosinophilia for a longer period of time.

This study has been reviewed recently and once again they conclude that GM-CSF for three years increases the survival in patients with a high recurrent risk of melanoma (HR = 0,61;

p = 0,047), but those on three years treatment have potentially causing AML, as it did happened in two patients. Immunological studies showed an increase of neopterin related to the macrophages activity that potentially could explain the mechanism of action of the therapy (Spitler et al. 2008). The Phase III study E4697 that compares GM-CSF versus placebo as an adjuvant treatment in staging III-IV melanoma that were excised, did included 815 patients (1999 to 2006), out of which 735 were eligibles. The overall mean survival rate was 72.1 vs. 59.8 months (p = 0.551) and the disease free survival was 11.8 vs. 8.8 months (p-0.034), with a minimum toxicity (Lawson et al. 2010). Undoubtedly the use of GM-CSF as monotherapy or in combination in adjuvance is a line of research that must be confirmed over the next few years.

2.7 Adjuvant radiotherapy

It is an option in melanomas with a high risk of regional recurrence after lymphatic clearance, specially in those cases with extra lymphatic extension, a positive lymph node greater than 3 cm, 4 or more positive nodes, residual disease or a Breslow's thickness equal or greater that 4mm. In a randomized study with 227 patients considered as having high risk of recurrence, 109 were included in the adjuvant radiotherapy group and 108 on the control group. After a mean follow up of 27 months, 20 patients had a recurrence in the radiotherapy group and 34 in the control one (p=0.0410), indicating a better control of the local recurrence with radiotherapy but not affecting the survival rate (Henderson et al. 2009).

3. New treatments

The lack of proven efficient treatments against metastatic melanoma affects the use of the adjuvant treatment. Chemotherapy, cytoquines, vaccines and combination treatments have been studied with little success. Only IFN has shown to be beneficial in DFS and in less degree in OS in high risk patients, therefore it is necessary to continue to research for new therapies. A new line of research has been found in the monoclonal auto-antibodies anti-CTLA-4 that block the interaction between B7 (B7-1 and B7-2 are homologous costimulatory ligands expressed on the surface of antigen presenting cells) and CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4), causing a negative inhibition that increases the citotoxicity of T-lymphocytes with antitumoral activity (Eggermond et al. 2010). At present, there are two monoclonal antibodies on phase II/III trials, use on their own or in combination: Ipilimumab and Tremelimumab.

Early-phase (I/II) clinical studies of tremelimumab demonstrated acceptable toxicity, mostly immune-related adverse events and similar efficacy of 10 mg/kg monthly and 15 mg/kg quarterly doses of the antibody with median survival times of 10.3 and 11 months, respectively. Both phase II regimens generated durable tumor response (Camacho et al. 2009).

Interesting data were presented at the 2010 annual meeting of the ASCO (American Society of Clinical Oncology), regarding the combination of Tremelimumab and HDI (High-dose Interferon alpha-2b) in a phase II trial in patients with metastatic melanoma. With an overall response rate of 30%, a progression-free survival rate at 6 months of 53%, and a median OS of 15.9 months, the results were very encouraging, especially since there seemed to be no added toxicity associated with the combination de Tremelimumab and HDI. Autoimmunity induced by therapy is significantly correlated with therapeutic benefit (Tarhini et al. 2010).

There are several studies in the last few years about metastatic melanoma and Ipilimumab as the only treatment and in combination with DTIC with survival rates of 11.5 and 13 months respectively. The presence of autoimmune reactions (diarrhoea, colitis and dermatitis) that can be controlled with steroids, can be used as a marker to asses the respond and duration of the treatment. A phase III study compares monotherapy with Ipilimumab and placebo (137 p.) versus Ipilimumab and vaccine gp100 (403 P.) versus placebo and vaccine gp100 (136 p.) in patients with stage III melanoma not excised or stage IV previously treated, with the main aim on the overall survival rate (OS). The mean survival was 10.0 months for the group that had Ipilimumab and gp100 and 6.4 months for the group that had gp100 alone (p=0.001). The survival of the patients who only had Ipilimumab was 10.1, also better that the gp100 alone group (p=0.003), not showing any differences between the groups with Ipilimumab. Immune reactions grade 3-4 were seen in about 10-155 of patients treated with Ipilimumab and 7 deaths were related to these side effects. In summary, Ipilimumab is the first drug that increases the survival in patients with advanced melanoma previously treated (Hodi et al. 2010).

The lack of benefit observed in stage IIIB/C with adjuvant IFN therapy was, for the EORTC Melanoma Group, the reason to move to a different drug. Thus, the EORTC 18071 pivotal adjuvant trial in stage IIIB/C, comparing a 3-years treatment with Ipilimumab to placebo in a double-blind randomized setting, was activated in 2009 and is expected to be completed in 2011.

4. Final comments

The reality is that except for data on IFN, no new validated strategies that improve results have come to the fore. The unquestionable increase of our understanding of the cell biology of melanomas leads to the idea of identification of sub-groups where the benefits would be greater. It is therefore absolutely necessary to identify new therapeutic targets, develop new drugs and make an optimal selection of patients. One of the most interesting targets is the analysis of the BRAF gene, mutated in 50-70% of melanomas, and furthermore associated with exposure to ultraviolet light. This mutation gives rise to a protein with a kinase activity about 500 times higher than the un-mutated protein thus enabling greater survival and proliferation of neoplastic cells. Sorafenib, a double target anti-angiogenic which inhibits BRAF on the one hand and VEGFR and PDGFR on the other, in association with CDDP in metastatic melanomas results in 13% PR and 53% SD. PD0325901 is another important inhibitor of the BRAF signal cascade (MEK1 and MEK2) and its efficiency has been tested in preclinical models as well as PLX40323 (Solid and Rosen, 2011). Nevertheless, the use of CTLA-4 inhibitors such as Ipilimumab and Tremelimumab, open new horizons in the treatment of melanomas and the future studies about adjuvant therapies, can change the prognosis, specially in high risk patients.

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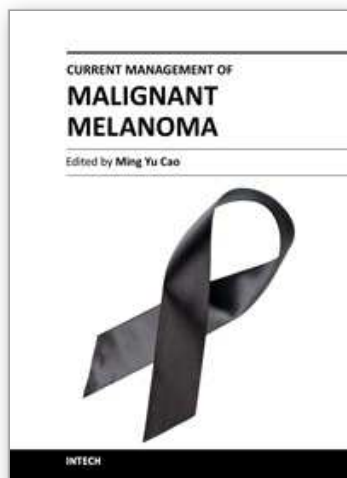
Current Management of Malignant Melanoma

Edited by Dr. Ming Yu Cao

Management of melanoma is challenging, especially for the late stage of the disease. Development of new therapies and optimizing current treatments are being pursued in attempt to further improve the survival rate. The book provides up-to-date knowledge and experience in early diagnosis, prevention and treatment of melanoma as well as current ongoing clinical studies on melanoma. The book also provides the most recent perspectives of research on the molecular basis of melanoma, such as melanoma associated genes and a possible link between stress and melanoma.

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