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The EORTC Melanoma Group: a comprehensive melanoma research programme by clinicians and scientists

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Abstract

The EORTC Melanoma Group (MG) was founded in 1969 by both clinicians and scientists from various disciplines and fields of research with a common interest in malignant melanoma. This collaborative approach has always been the foundation of the groups strength. With an interest in tumour biology and especially the immunological aspects of the disease, the group has always pursued a scientific approach to treatment development in malignant melanoma. Over the years, the group has performed many clinical trials, epidemiological studies, histopathological studies defining standards and guidelines, translational research regarding prognostic factors and various metastatic and immunological aspects of melanoma, and developed quality assurance programmes for immunological and molecular biological assays in laboratory networks. At present, the EORTC MG runs the worldwide largest clinical trial programme in stages II, III and IV melanoma involving some 140 cancer centres in and outside Europe. Each trial is associated with the appropriate translational research programmes. © 2002 Published by Elsevier Science Ltd.

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1. Introduction

Thirty-two years ago the EORTC Melanoma Group was founded in 1969 by a group of clinicians and scientists from various clinical disciplines and fields of research. The common denominator of interest was melanoma and the immune response. Over the years, a comprehensive clinical–pre-clinical research programme has evolved ranging from clinical studies to development of assays to detect cytotoxic T-cells, circulating tumour cells, to large epidemiological studies.

2. Principal achievements

2.1. Clinical trials

The EORTC MG has carried out a large number of randomised phase III trials trying to identify effective adjuvant therapies for primary melanoma with a high risk for relapse. Moreover, a number of trials in stage IV metastastic melanoma have addressed the utility of various biochemotherapeutic regimens. The adjuvant therapy trials are summarised in Table 1, the trials in stage IV melanoma are summarised in Table 2.

2.2. Surgery

The most important clinical trial regarding the surgical management of high-risk primary melanoma has been the *EORTC18832* trial comparing the outcome of wide excision versus wide excision plus prophylactic

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Table 1
Adjuvant therapy trials in stage II-III melanoma by the EORTC melanoma group

Trial	Stage	Patients	Design	Outcome	Ref.
Surgery					
18832	II	832	WE	NS	[1]
			WE + ILP	No more prophylactic ILP	
Adjuvant systemic therapy in stages II-III					
18721	II	–	HD BCG	STOPPED (“unethical”)	
			LD BCG		
			Observation		
18761	II	326	Levamisole	NS	[2]
			Observation		
			DTIC + levamisole		
			Observation		
18781	II	354	BCG strain A	NS	[3]
			BCG strain B		
18871	IIB/III	830	IFNα2b	NS	[4]
			IFNγ		
			Iscador		
			Observation		
18952	IIB/III	1418	IFNα2b 10 MU, 1 year	NS	
			IFNα2b 5 MU, 2 years	$P<0.015$ DMFI	[4]
			Observation		
18961	II	1300	Vaccination GM2	Ongoing	[6]
			Observation		
18991	III	900	PEG-IFNα2b, 5 years	Ongoing	[5]
			Observation		

WE, wide excision; ILP, isolated limb perfusion; IFN, interferon; MU, million units; DMFI, distant metastasis-free interval; NS, non significant.

Table 2
Trials of the EORTC melanoma group in stage IV melanoma

Trial	Patients	Design	Outcome	Ref.
18931	138	IL2/IFNα		[10]
		IL2/IFNα + CDDP	RR: $P<0.02$	
			TTP: $P<0.04$	
			OS: NS	
18951	363	DTIC/CDDP/IFNα	RR: NS	[13]
		DTIC/CDDP/IFNα + IL2	TTP: NS	
			OS: NS	
18951 (Add)	100	DTIC		
		DTIC/CDDP/IFNα + IL2	ongoing	
18981	256	TMZ	ongoing	
		TMZ + XRT brain		

Ref. = reference; RR, response rate; TTP, time to progression; OS, overall survival; IL2, interleukin-2; IFN, interferon; CDDP, Cisplatin; DTIC, dacarbazide; TMZ, temozolomide; XRT, radiotherapy; NS, non significant.

isolated limb perfusion (ILP). Macroscopic in-transit metastases are known to develop in 5–8% of the patients with a high-risk primary melanoma. Retrospective studies suggested, as studies using historical control invariably seem to do(!), that a prophylactic ILP (just like elective lymph node dissection) improved outcome in patients with high-risk primary melanoma. The only valid and definitive trial addressing the question of the value of a prophylactic ILP with melphalan in the management of high-risk primary melanoma of the extremity is the intergroup trial of the EORTC with the World Health Organization (WHO) and the NAPG (North American Perfusion Group). Over a period of 10 years, 852 patients were randomised of which 832 were evaluable. At a median follow-up of >6 years, a definitive analysis was performed [1]. ILP had only a regional effect and a significant reduction in the appearance of in transit metastases was noted (reduction from 6 to 3%). A reduction of regional lymph node metastases (or a delay in their appearance) was noted without any effect on the appearance of distant metastases. Thus, prophylactic ILP had absolutely no effect on overall survival. It is a harmful procedure with significant morbidity and costs and without any impact on survival. As a result of this EORTC intergroup trial, prophylactic ILP is now no longer performed.

2.3. Adjuvant systemic therapy trials

The EORTC-MG has conducted a number of important randomised phase III trials in patients with thick primary melanoma (stage II) and patients with regional lymph node metastases (stage III). These adjuvant trials have focused on the use of immunostimulants such as BCG, levamisole, and interferons. Interestingly, the first trial, the *EORTC18721*, which compared the effects of two different doses of BCG versus observation in stage

II–III melanoma, was stopped because "withholding BCG from patients with high-risk melanoma was unethical" in the eyes of the public in the early 1970s! Many trials since then have demonstrated that BCG has no significant impact on disease-free survival or overall survival in the adjuvant setting in high-risk melanoma. Similarly negative results were obtained in the *EORTC18761* trial [2] comparing treatment with DTIC versus levamisole versus DTIC + levamisole versus observation in stage II melanoma and in the *EORTC18781* comparing adjuvant therapy with different stains of BCG in the same clinical setting [3].

The *EORTC18871* trial [4], was the first interferon-alpha trial conducted by the EORTC MG to evaluate the effectiveness of ultra-low dose rIFN-α2b (1 MU) or rIFN-γ (0.2 mg), both subcutaneous (s.c.), every other day for 12 months in comparison with an untreated control group. The *German Cancer Society (DKG),* added a fourth arm with *Iscador M*®, a popular mistletoe extract. Into this trial, 830 patients were randomised and when followed for a median of 5.5 years, the analysis showed no significant impact regarding either the DFI (logrank $P = 0.64$) or the duration of survival (logrank $P = 0.72$) being observed for any of the treatments evaluated.

After the ultra-low dose IFN-alpha trial 18871, the group embarked upon a trial, *EORTC18952*, evaluating the efficacy of thus far unexplored intermediate doses of IFN-alpha, in the hope to define a threshold level for activity of IFN at tolerable doses. EORTC 18952 is the largest and fastest accruing adjuvant therapy trial ever conducted in melanoma. Within a period of 4 years, 1418 melanoma patients (stage IIB-III) were randomised. Treatment with IFNα consisted of an induction period of 4 weeks, 5 days/week, 10 MU, s.c. is followed by a maintenance period of 10MU, s.c., tiw for 1 year versus 5 MU, s.c., tiw, for 2 years, versus observation. The first analysis was reported at the 37th Annual Meeting of the American Society of Clinical Oncologists (ASCO) in 2001 [4]. The analysis indicates that duration of treatment is more important than dose of IFNα, since the higher dose of 10 MU for 1 year had no significant impact on 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 DMFI ($P = 0.0145$). These data should be interpreted with the greatest caution as many 'early positive reports' have seen the light in the history of phase III trials. If the impact on DMFI translates into a similar impact on overall survival, this schedule for 2 years may be accepted in Europe, since its toxicity profile with grade 3–4 events in about 10% of patients is reasonable. It is clear that, with mature results pending in three major adjuvant trials in some 3000 melanoma patients, of which the EORTC 18952 trial is the biggest, the role of IFNalpha in the adjuvant setting in melanoma still remains to be determined [5]. Importantly, these results of trial 18952 support the trial design of the currently ongoing *EORTC18991* 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 [5].

The hypothesis is based on the observation that IFN therapy has a consistent impact on DFS regardless of dose and that long-term treatment may be more important than dose, as well as on the anti-angiogenic mode of action of IFNα.

Because of sentinel node staging, the prognosis of SN-staged node-negative stage II patients has improved enormously. This stage migration has led to the position in the EORTC MG that IFNα is an agent that is associated with too much toxicity to be evaluated in this patient population [6]. Therefore, stage II patients are randomised between vaccination with the ganglioside GM2-KLH/QS-21 versus observation (standard of care) in the currently ongoing *EORTC18961* Trial in 1300 patients, a trial that in 1991 had already found its rationale based on an EORTC MG study [7].

2.4. Translational research

The prognostic value of sentinel node staging, the methodology of analysis of the SN and its value as a prognostic factor relative to old and other new prognostic factors such as S100, TA-90 and possibly angiogenic factors, are the topic of translational research projects in association with the adjuvant therapy trials 18952, 18961 and 18991 [8]. A project on the (negative) sentinel nodes of stage II patients will compare assessment by Haematoxylin and Eosin (H&E) staining to immunohistochemistry (IHC) to Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) with various markers and will identify inside this prospective large database the "false-negative rate of standard SN-work-up", the relative accuracy of each method, and its correlation to relapse and survival. In SN-positive stage III patients, a similar work-up of the top lymph node of the regional lymph node dissection will give an indication of the accuracy of each methodology to detect lymph nodal spread beyond the SN and its prognostic significance. These findings will be correlated to the results of sequential blood sample testing for circulating tumour cells by RT-PCR and serum tumour marker measurements such as S100, TA-90 and Angiostatin. Moreover SN-positive and -negative nodes will be assessed for the presence of activated cytotoxic T lymphocytes (CTLs) and downregulation of dendritic cell functions, as reported by Cochran to be present in tumour-containing SNs. SN-staging is an excellent tool to conduct 'cleaner' trials by studying more homogeneous and better defined patient populations [8,9].

2.5. Trials in stage IV

Interleukin-2 has (IL2) been a key cytokine in the randomised phase III trial programme of the EORTC MG, using the 'decrescendo regimen', developed by Keilholz and coworkers.

In the *EORTC18931*, the efficacy of this regimen with IL2 + IFNα was compared with IL2 + IFNα + CDDP (100 mg/m^2 on day 1). In spite of a significantly higher response rate (15% versus 33%; $P < 0.04$), as well as a significantly prolonged time to progression (53 versus 92 days; $P < 0.02$) in the CDDP-containing arm, median survival was identical in both arms (9 months). Survival at 2 years was about 15% in both treatment arms [10]. This outcome is in line with the results of several trials that have failed to show an impact on survival by adding or expanding chemotherapy regimens in stage IV melanoma. In a case record-based database set up by the group, in an analysis of 631 patients treated with IL2-based regimens [11,12] the following observations emerged regarding Response Rates (RR). In the four groups of patients: IL-2 alone ($n = 117$; RR = 14.9%; non significant (NS)), IL2 + chemotherapy ($n = 49$, RR 20.8%; NS), IL2 + IFN ($n = 153$; RR = 23.0%; NS) and IL2 + IFN + CTX ($n = 312$; RR = 44.9%; $P < 0.001$). Median survival rates did not differ significantly: IL2 versus IL2 + chemotherapy (7.5 versus 9.9 months); IL2 + IFN versus IL2 + IFN and chemotherapy (10.5 versus 11.4 months). 2- and 5-year survival rates were for IL2 12 and 4%; for IL2 + chemotherapy 13 and 8%, and much better for IL2 + IFNalpha 24 and 14%, while no further improvement was observed in IL2 + IFN + chemotherapy (22 and 12%). These findings suggest that a long-term survival benefit may mediated by IL2 (+ IFN)-based therapy.

The question of whether IL2 is the crucial component is addressed in *EORTC18951*: DTIC + CDDP + IFNα vs DTIC + CDDP + IFNα + IL2 in 363 patients. This trial was analysed at the end of the year 2000 and showed similar response rates (24% versus 22%), time to progression rates, median survival times (8.5 months), as well as similar 2-year survival rates (15% versus 15%) for both arms and thus failed to show an improved outcome mediated by IL2 [13]. The definitive analysis will be conducted end of 2001. This trial has been extended by an amendment which evaluates randomisation between treatment with either DTIC alone or the four-drug combination DTIC/CDDP/IFN/IL2 for two treatment cycles, whereby patients with stable disease (S.D.) or better are eligible for two more cycles of treatment with the four-drug regimen.

The ongoing trial *EORTC18981* evaluates whether the addition of radiotherapy improves the therapeutic effect of orally administered TMZ of stage IV melanoma with *asymptomatic* brain metastases in terms of overall survival. Secondary end-points are the duration of the period free of neurological symptoms, progression-free survival, quality of life and toxicity.

2.6. Studies of the Pathology Committee

The pathology committee has played an important role in setting standards for central pathology review and quality assurance for the EORTC MG trials and has published a number of important papers on criteria and guidelines in the field of dysplastic naevi [14], melanoma in childhood [15] and melanoma staging systems [16]. The diagnosis of melanoma in childhood is marred with pitfalls and the diagnosis is often incorrect. In a review/reassessment of >100 cases by the EORTC-MG pathologist-panel it was concluded that in almost half the cases the diagnosis melanoma was incorrect [16]. At present, the EORTC-MG is a full partner in the EU telematics project that aims to improve exchange of diagnostic images through a European network.

Another focus of studies performed by the pathology committee has been the expression of various classes of antigen in primary, regionally metastatic and distant metastatic melanoma. The EORTC MG carried out the most extensive inventory study on the use of monoclonal antibodies in the early 1990s [17] and documented changes of expression under cytokine treatments [18]. The differential expression of antigens in relation to the progression of the disease was shown to have important implications for both diagnosis, as well as immunotherapeutic treatment strategies [19]. In yet another study on the EORTC MG primary melanoma material it was demonstrated that high tPA-expression in primary melanoma of the limb correlates with good prognosis [20].

2.7. Studies of the Epidemiology Committee

An increasingly important part of the comprehensive melanoma programme of the EORTC MG has been the epidemiology committee programme regarding risk factors (especially of a behaviourial nature) for the development of malignant melanoma. Already in the early 1990s consensus meetings on primary and secondary prevention of melanoma were organised by the group [21]. Highly original study designs have evaluated the risks associated with sunscreens and sunlamps and sunbeds. Some very important findings demonstrated by these epidemiological studies have been that the use of sunscreens may rather increase the risk for development of melanoma than protect against it [22]. Psoralen-containing sunscreens were identified as outright increasing the risk for melanoma development, and such sunscreens were subsequently banned from the EU-market [22,23]. Ultraviolet (UV)-light protection during childhood and early adulthood were identified as key in the prevention of melanoma [24] and furthermore

that a naevi-count in children is an excellent surrogate marker for UV-exposure intervention studies and thereby for melanoma risk assessment [25,26]. In a randomised trial, it was demonstrated that sunscreen use with high UV-protection increases subconsciously the sunbathing time and exposure to UV-light and may thus increase rather than decrease the risk for melanoma development [27].

2.8. Studies of the Laboratory Sciences Committee

The laboratory sciences committee of the EORTC MG has worked on cytotoxic lymphocyte assays development and standardisation over the last decade. Of particular importance has been the Elispot assay programme, which was launched by workshops and executed through a validation programme in which various laboratories participated [28]. At present, a similar programme is launched regarding tetramere methodology in this field. Moreover, workshops on immune monitoring in vaccination trials have been organised by the EORTC MG.

A similar approach was used regarding the standardisation of RT-PCR methodology to detect circulating tumour cells [29].

2.9. Intergroup activities

2.9.1. EORTC Uveal Melanoma Programme of Clinical Research

Uveal melanoma is a rare disease (6–8 cases per one million in the caucasian population) and trials in such an 'orphan disease' should be handled by a network of highly-specialised institutions. This disease is consequently of limited commercial interest to private pharmaceuticals companies, due to the absence of adequate (potential) return of investment for two main reasons: (a) small marketing/commercial target patient population; (b) important financial investments in clinical trials to be conducted in numerous institutions/countries in order to obtain an adequate patient accrual.

This is the reason why, within the framework of the EORTC Melanoma Group and in co-operation with the EORTC Ophthalmic Oncology Task Force, a specific programme of clinical research fully devoted to promote pilot studies for new therapeutic developments in uveal melanoma, has been set up recently. Specific quality assurance criteria have been selected both within the Melanoma Group and the Ophthalmic Oncology Task Force networks, to select high quality institutions capable of managing drug and vaccine development in this disease, to collect clinical data in an adequate timeline and to initiate specific translational research projects. This resulted in the creation of a specific network of more than 30 institutions in 10 European countries, which should be able to conduct high quality phase II and phase III studies. Because of a current lack of financial support for this 'orphan disease', this specific programme would not be possible without the full support of the EORTC Board, as the large majority of the clinical studies in the project are non-financed academic studies.

2.9.2. Recent achievements

The first clinical study of the EORTC Uveal Melanoma Programme is also the first pan-European phase III Vaccination Study with specific tumour antigens. The *EORTC 18001–88001* study assesses the value, in terms of distant metastasis-free survival, of vaccination with the NA17.A2 and melanoma differentiation peptides in HLA-A2 patients with primary ocular melanoma treated locally by surgery and/or radiotherapy. Important translational research projects will be performed in parallel, including the analysis of: (1) immune response to the vaccine (tetramers and Elispot); (2) HLA-A2 expression by immunohistochemistry and by RT-PCR following laser dissection on the resected tumour; (3) monosomy 3 on the resected tumour.

A phase II randomised study of intravenous versus intra-arterial fotemustine chemotherapy in metastatic uveal melanoma patients is currently processed and should be open to recruitment in a few months. Again, this study will involve highly specialised centres (intra-arterial catheter technique).

2.10. Perspectives

Rhe EORTC MG is committed to further execute and expand a comprehensive melanoma programme through the fully integrated and collaborative approach by its member scientists and clinicians. Molecular therapeutics and vaccine development will be an important focus for the next decade as is the ever challenging task of identifying a systemic adjuvant therapy regimen for high-risk melanoma that is effective enough to be accepted as standard of care and a stepping stone for further developments. In the field of epidemiology studies, the time for a molecular epidemiological programme has arrived and innovative studies will be launched in that field. The membership of the group will grow further and incorporate especially scientists from fields of research such as genetics and genomics. The EORTC MG is thus headed for even more existing times in its existence.

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