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# Introduction

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THE INCIDENCE of melanoma continues to increase at a rate exceeding that of other solid tumours. Melanoma comprises 10% of all skin cancers, yet it accounts for 80% of skin cancer deaths. In addition, melanoma results in more years of life lost per case than any other malignancy, including breast and lung cancer. Medical treatments for this disease have previously yielded disappointing results. Patients with deep primary tumours or regional lymph node involvement have rates of disease relapse and mortality ranging from 50 to 90%. Fortunately, our understanding of the molecular biology and immunology of melanoma has progressed substantially, leading to the introduction of innovative strategies for the management of this disease that have shown an ability to alter the natural history of melanoma.

On 27 and 28 February 1997, more than 600 oncologists and dermatologists attended a major educational symposium held in Barcelona to review and discuss various aspects of the diagnosis and treatment of melanoma. Presentations by a renowned faculty included discussions of lymphatic mapping and sentinel node biopsy, the potential for detection of circulating melanoma cells, management of the disease using interferon alfa-2b (IFN-α2b), new immunomodulating strategies including cytokines and vaccines and the evaluation of these new agents in cooperative group trials. These presentations are collected in this supplement.

Dr MacKie (pp. S3–S6) discusses trends in melanoma incidence that have been identified by the Scottish Melanoma Group. This group has collected data on more than 8000 melanoma patients since 1979. Overall, the incidence of melanoma and associated mortality have increased between 1940 and 1990 in both males and females. However, for Scottish females younger than 65 years, the incidence appears to have peaked and mortality has decreased. These findings may be the result of earlier diagnosis and treatment of melanoma in response to public education efforts. The role of new treatments is unclear at this time, but deserves evaluation if these trends continue. The development of effective treatment for melanoma patients before metastases occur remains vital to reducing morbidity and mortality associated with this disease.

A challenging problem in the management of patients with early stage melanoma is the detection of micrometastases to regional lymph node basins. The presence of clinically undetectable nodal disease is an important prognostic factor. Traditionally, these patients were either monitored closely for clinical signs of disease spread or lymphadenectomy was performed. Dr Ross (pp. S7–S11) provides an overview of a new technique that allows selective lymphadenectomy for node-positive patients only. Lymphatic mapping identifies the lymph node most likely to contain disease, or the sentinel lymph node, which is biopsied and if positive, lymphadenectomy is performed. This technique appears accurate and valuable for staging melanoma patients.

Patients with deep primary melanomas or node-positive disease are at greatest risk of disease relapse. The results of the Eastern Cooperative Oncology Group (ECOG) trial 1684 represent the first evidence of effective adjuvant therapy for these patients; IFN-α2b administered at maximally tolerated doses for 1 year significantly improved both relapse-free and overall survival. The therapeutic impact was observed early and remained durable over a median follow-up period of 7 years. These results have important potential implications for the immunologic treatment of melanoma and encourage further research with vaccines, using interferon therapy as the reference standard and a potential means to enhance vaccine efficacy for melanoma.

Although ECOG 1684 did not include a prospective analysis of quality of life or cost efficacy, retrospective studies have been conducted to address these areas of interest following the observation of antitumour efficacy. Dr Hillner (pp. S18-S21) reviews the results of a cost-effectiveness analysis of IFN-α2b therapy. A hypothetical cohort of melanoma patients whose mean interferon dosage and clinical results were extrapolated directly from the results of ECOG 1684 was evaluated. The economic model predicted that IFN-α2b provided an extra 0.52 years of life compared with observation at 7 years and an anticipated 2 years of survival benefit at 35 years of follow-up. The costs of treatment were comparable to those of other well-established medical interventions. Adjuvant IFN-α2b results in substantial benefits in survival and quality-adjusted survival that appear to be cost-effective.

Based on these results with high-dose IFN-α2b and those examining other dosage regimens of interferon and other immunomodulators, the European Organization for Research and Treatment of Cancer (EORTC) has developed a trial programme of IFN-α2b immunotherapy for the treatment of melanoma. For patients with high-risk disease (stage IIB–IIIB) two intermediate dosages of interferon and observation

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are being compared. This trial includes prospective analyses of quality of life and cost-effectiveness and will attempt to discover an active regimen of IFN-α2b that is less toxic, simpler and thus less costly and more widely applicable than high-dose IFN-α. For patients with moderate-risk disease (stage IIA), vaccination with ganglioside GM2 is being compared with observation. Completed ECOG studies include the E1690 comparisons of the high-dose E1684 interferon regimen with prolonged low-dose IFN-α2b or observation in stage IIB–IIIB patients. Current ECOG studies include the intergroup E1694 phase III trial of GMK vaccine therapy versus the standard high-dose IFN-α2b regimen and a phase II trial examining the effects of vaccine GMK alone, versus GMK with concurrent or sequential use of IFN-α2b at high-dosage.

The treatment of metastatic disease remains a challenge, with no improvement in survival over the last 20 years. Dr Rusthoven (pp. S31–S36) reviews clinical trial data evaluating the use of tamoxifen with or without antineoplastic agents for metastatic melanoma. Overall, response rates from numerous phase II and III trials range from 8 to 60%. Data presented by Dr Rusthoven argue persuasively against the use of tamoxifen in combination with cisplatin-containing regimens for metastatic melanoma. Any remaining questions regarding the value of tamoxifen in conjunction with the Dartmouth polychemotherapy regimen will potentially be put to rest with the completion of the current intergroup M91–140 trial involving ECOG and Memorial-Sloan Kettering Cancer Center (New York, U.S.A.). Dr Pyrhönen (pp. S27–S30) presents treatment options for metastatic uveal melanoma, which results in metastases in 20 to 35% of patients within 5 years and has a unique pattern of distribution favouring the liver. The disease is resistant to treatments used for metastatic cutaneous melanomas and no standard exists. Hepatic artery embolisation or chemoimmunotherapy regimens appear to be active in phase II trials. An extended multicentre study has been initiated to examine the combination of interferon and four antineoplastic agents in the treatment of this disease.

The future of melanoma treatments may be further enhanced with recent molecular discoveries. Particularly, the ability to monitor the presence of circulating tumour cells is described by Dr Keilholz (pp. S37–S41). Polymerase chain reaction assays offer the greatest sensitivity for tumour dissemination and minimal residual disease, an important prognostic factor for melanoma patients. Studies are ongoing to determine the clinical value of such determinations.

Specific immununotherapy for melanoma treatment also is possible with the discovery of T-cell recognised tumour-associated antigens. More than 30 peptides have been cloned and studies investigating their use are reviewed by Dr Parmiani (pp. S42–S47). Results of clinical trials are highly variable but encourage further research. A key aspect in determining the role of vaccines intended to stimulate T-cell responses is the development and validation of laboratory and clinical correlates of response.

Important progress has been made in the diagnosis and treatment of melanoma including the ability to accurately identify lymph node status and selectively perform lymph node dissections, evidence of effective adjuvant therapy with IFN-α2b that prolongs disease-free and overall survival in patients with high-risk resected cutaneous melanoma and identification of tumour antigens and the genes that encode these antigens. This supplement provides a comprehensive review of these recent developments and their impact on our knowledge and approach to the treatment of melanoma.