Introduction

Optimal approach for melanoma

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The incidence of cutaneous melanoma is rising faster than that of any other malignancy, and in some parts of Europe it is now the commonest cancer outside of “the big four” common malignancies: i.e. breast, lung, colorectal and prostate cancers. There is little doubt that the major factors in the development of melanoma are skin type, racial origin and sun exposure. Short sharp bursts of sunlight leading to sunburn are dangerous, especially when they occur in children and adolescents.

Ten percent of melanomas are familial in origin, and as with other cancers, the biology associated with such tumours has helped us to develop an understanding of the molecular genetics of sporadic melanoma. A number of mutations have been described, including those found in CDKN2A, CDK4, RB1, p14ARF, NRAS and particularly BRAF. BRAF mutations are found in approximately 50% of patients with cutaneous melanoma, and the development of targeted agents against mutations in BRAF has been responsible for one of the most dramatic examples of molecular medicine in oncology.

Adjuvant therapy for patients at high risk of relapse following treatment for primary melanoma or locoregional disease remains an area of uncertainty. The use of adjuvant interferon, at various doses and schedules, has been the subject of many randomised trials over 25 years. It is of note that some large trial groups such as those in Europe still feel that there is enough uncertainty as to the efficacy of interferon that randomised trials of adjuvant therapy should still be performed with a no-treatment control arm. The one indisputable fact about adjuvant interferon is that it is associated with a relapse-free survival benefit, but some argue that, unlike treatment in the metastatic setting, the purpose of adjuvant therapy is to improve overall survival. A number of meta-analyses of the randomised trials involving interferon have been published, and it appears that the maximum absolute benefit to overall survival is in the order of 2–3% and again, some argue that this is below the threshold of useful clinical utility. Randomised trials of the newer melanoma therapies are now being brought into the adjuvant arena.

Vemurafenib is a BRAF inhibitor, and the results of the first randomised trial of vemurafenib against standard of care – namely, dacarbazine (DTIC) – were dramatic in terms of response rates, progression-free survival and overall survival. The hazard ratio for overall survival at the time of the first analysis was unprecedented in solid tumour oncology. The therapeutic momentum has continued with the development of MEK inhibitors and their combination with BRAF inhibitors. Other targeted therapies are being developed for uveal and acral melanomas, e.g. against c-KIT mutations in the latter.

The most important recent development in immunotherapy has been the targeting of inhibitors of the immune system, e.g. CTLA-4, PD-1 and its ligand PD-L1. Ipilimumab targets CTLA-4 and is the first immunotherapy to have shown an overall survival benefit in melanoma within the context of a randomised trial. The magnitude of benefit can be very great in some patients with prolonged complete remissions; however, it is only a minority of patients that benefit. Early results targeting PD-1 and PD-L1 are particularly exciting because they appear to challenge the dogma that immunotherapy only impacts a minority of patients. Early results suggest that the majority of patients show some benefit without necessarily achieving a complete remission.

The new immunotherapeutic landscape means that our previous view of follow-up needs to change rapidly. We now know that there is an important immunotherapy that is associated with a survival advantage, but that, as with most immunotherapies, it can take some time before the host response becomes effective. This time-frame may be 2–4 months, and therefore it is completely illogical to wait for a patient to become symptomatic from their metastatic disease before investigating and treating them.

Patients must have their metastatic disease diagnosed early, otherwise there is little prospect of a successful outcome to immunotherapy, and therefore patients at high risk of relapse need regular imaging, and treatment should be instituted before high volumes of disease are seen.

Conflict of interest statement

Speaking bureau, Advisory Boards: Pfizer, Roche, Bayer, Novartis, Bristol Myers Squibb, Astellas.

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