New and standard management of malignant melanoma

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Surgical management

Margins

Failure of wide margins to improve survival

The concept of a 5 cm margin of excision was challenged following Breslow' s demonstration that prognosis was related to the thickness of the primary lesion. Three trials were conducted in patients with thin melanomas <2 mm, randomising patients in one trial to margins of 1 cm versus 3 cm or 2 cm vs 5 cm in two other trials. In the USA, patients with 1–4 mm melanomas were randomised to 2 cm vs 4 cm margins. The outcome in all trials showed similar local recurrence rates, disease-free survival (DFS) and overall survival (OS) after narrow and wide excision [1]. The recent UK-MSG trial [2] compared margins of 1 cm with 3 cm for melanomas >2mm. It showed higher locoregional recurrence rates in the 1 cm arm, but again no difference in overall survival. Thus a 1cm margin is adequate for melanomas <2 mm and a 2 cm margin for melanoma >2 mm. Smaller margins are allowed on distal extremity sites and in the head and neck area. This means that split skin grafts are rarely if ever necessary.

Regional lymph nodes

Failure or elective lymph node dissections to improve survival

It is acknowledged that lymphatic spread usually occurs concurrently with hematogenous metastasis in most solid tumours including melanoma, and that lymph node metastases are ' indicators rather than governors of survival' [1]. Four randomised trials evaluated whether elective (immediate) regional lymph node dissection (ELND) results in improved survival [1]. All four trials failed to demonstrate a survival benefit for ELND and as a result ELND was largely abandoned in Europe. The WHO-14 trial suggested that patients with micrometastases in lymph nodes after ELND had an improved survival compared to those after a delayed lymph node dissection for clinically positive nodes. These data seemed to support the implementation of sentinel node biopsy [3] as an ideal staging procedure.

Sentinel node (SN) biopsy

SN staging is based on the now well-supported hypothesis that melanoma lymphatic metastases follow an orderly progression through afferent lymphatic channels to SNs before spreading into other regional, non-sentinel nodes.

SN-status is strongest prognostic factor

SN-status is the strongest prognostic factor in melanoma patients. Literature studies demonstrate 5-year overall survival (OS) rates of 93% and 89% for SN negative patients, and OS rates of between 67% and 64% for SN positive patients.

No proof that SN staging provides survival benefit

Whether SN staging has an impact on survival remains to be seen – a recent study by Doubrovsky and colleagues [4] show that SLNB is superior to ELND due to differences in histopathological protocols to examine the lymph nodes. However SLNB patients had no survival advantage compared to ELND patients in this matched control study. More importantly the interim analysis of the MSLT-I trial does not suggest any survival benefit for SN-staging in the overall population with high-risk primary melanomas. Survival rates at 5 years are 87% and 86% respectively, whether or not a SN procedure has been performed [5].

Whether a complete lymph node dissection at the time of the identification of a positive SN improves on survival is unclear at the moment as well. Although the survival rates in the SN-positive patient population at 5 years are reported to be higher than in the patients that did not undergo SN-staging and had a delayed lymph node dissection (DLND) later because of developing clinically positive nodes, it should be realised that this is not a strictly randomised comparison and it may well be that patients who develop clinically positive disease represent a biologically unfavourable selection of patients as compared to the complete set of SN-node positive patients [5].

No proof that SN-staging enhances locoregional recurrence rates

Some reports have assumed an increased rate of in-transit metastasis after the SN procedure [6]. There were however important imbalances in primary tumour characteristics such as Breslow thickness and ulceration in these studies. Studies with much larger case numbers demonstrate that the increase in the in-transit metastasis rate is not real, but due to a prolonged recurrence-free interval. Since the SN procedure avoids nodal recurrences, it increases the chance of in-transit metastases to manifest as a first recurrence site. The overall in-transit probability however remained unchanged, independent of whether early or delayed excision of nodal metastases is performed [7]. SN staging is quite useful for stratifying patients in randomised systemic adjuvant therapy trials, to create more homogeneous patient populations to determine whether adjuvant systemic therapies are of benefit [8] SN-staging may improve long-term locoregional control in the lymph node basin compared to the patients who undergo DLND [5]. It is however clear that ultrasound of the regional lymph nodes may also be able to achieve this by detecting very small non-palpable lymph node metastases, thus offering an alternative to a SN-procedure [9].

In-transit metastasis

Failure of prophylactic ILP to improve survival

Prophylactic isolated limb perfusion (ILP) as an adjunct to the surgical management of patients who are at high risk of relapse was popular in Europe because retrospective studies had suggested improved outcomes. The large intergroup trial (EORTC 18832/WHO-15) randomised 832 patients and demonstrated that prophylactic ILP had a regional effect with a reduction in the incidence of in-transit metastasis from 6.6% to 3.3% and a reduction in regional lymph node metastases from 16.7% to 12.6%. However, there was no effect at all on distant relapse-free or overall survival. So prophylactic ILP is no longer performed or reimbursed in Europe. TNF-based ILP is successful in treating highly morbid symptomatic in-transit metastasis. In contrast ILP, especially when melphalan is combined with TNF, is highly effective in the symptomatic setting of multiple or bulky in-transit metastases, with CR rates of 70% and in the treatment of melphalan ILP failures with similarly high CR rates [10].

Conclusions

In conclusion, phase III randomised trials have shown that wide margins, elective lymph node dissections, sentinel node biopsy, and prophylactic isolated limb perfusions have not improved survival and cannot be considered standard of care in the routine management of primary melanoma.

Systemic adjuvant therapies

Thus far chemotherapy, aspecific immunostimulants and vaccines have all failed

Some 25 trials have been conducted evaluating chemotherapy or aspecific immunostimulants such as BCG (Bacillus Calmette-Guerin), *C. parvum* (*Corynebacterium parvum*), Levamisole or combinations of these agents with Dacarbazine in stage II–III melanoma. The trials were almost invariably underpowered yielding negative results with the exception of incidental non-repeatable small-sized positive trials [1]. None of the five randomised trials with allogeneic melanoma cell-based vaccines has demonstrated a significant impact on survival. A small trial with the ganglioside GM2 did show a benefit but only in a subset analysis of stage III patients who were seronegative for ganglioside antibodies prior to trial entry. This study led to the currently ongoing EORTC18961 trial in stage II patients. The Melacine vaccine showed encouraging results in patients with particular HLA-types. A big vaccination trial awaiting analysis is the Canvaxin trial in patients with stage III disease. In patients with resected stage IV however an interim analysis stopped further accrual because of the absence of an indication of impact of the Canvaxin vaccine.

Adjuvant therapy with interferon-alpha is an ongoing controversy

Although the use of high-dose interferon (HDI) therapy is approved by both the FDA and EMEA for high risk melanoma (stage IIB–III) it is used very little in Europe. The reason for this is the lack of proof of impact on overall survival, in spite of an impact on disease-free survival (DFS). Pooled data analysis of HDI trials [11], meta-analysis of phase III trials [12] demonstrated consistent DFS improvement but no significant improvement on overall survival (OS). Low dose IFN (LDI) therapy has demonstrated less impact on DFS in stage III and consistent improvement of DFS in stage II, but never improvement of OS. In spite of this, LDI was approved for stage II by the EMEA in Europe while refused by the FDA in the USA.

Meta-analysis confirmed an impact on DFS but no impact on OS for LDI, and its use can not be justified on the basis of the lack of evidence of worth while activity. Intermediate doses of IFN (IMI) were tested in the largest phase III trial to date (EORTC18952) and demonstrated some, but not statistically significant activity (7.2% increase of DFMI; 5.4% increase of OS at 4.65 yrs follow up) for 25 months of 5MU and no effect for 13 months of 10 MU therapy in stage IIB–III disease [13]. All in all IFN failed to demonstrate significant impact on OS in stage IV as well as in the adjuvant setting. The quest to identify the subpopulation of melanoma patients that do benefit from IFN therapy and thus the role of IFN remains to be determined [14].

Conclusions

The lack of effective drugs in stage IV disease is reflected by a lack of effective adjuvant therapies in stage II–III melanoma. Thus far, chemotherapeutic drugs, immunostimulants and various vaccines have all failed. IFN has some effect, but it is judged by many to be too small to be considered standard of care. The population of patients that can benefit from IFN needs to be identified by genomics and proteomics studies, which are ongoing. The potential value of long term maintenance therapy with Pegylated IFN (EORTC18991) or by the Canvaxin vaccine awaits analysis in 2006.

Systemic therapies for stage IV disease

There is no effective systemic therapy for metastatic melanoma

Even the response rate to the ' standard' drug dacarbazine is probably inferior to 10% and no treatment is good enough to be considered standard of care [15]. Polychemotherapy, addition of tamoxifen, interferon, interleukin-2 have all failed to improve survival in more than 15 phase III trials [15]. Different agents should be offered as first-line therapy to stage IV melanoma patients to identify active new agents. Moreover vaccine therapy trials have yielded very low response rates and no indication of any impact on survival [16]. The anti-CTLA4 antibody may be important alone, or in combination with cytokines and vaccines, as it fundamentally changes the balance between T-helper and T-supressor cells. It can also change the immune response and immune status of melanoma patients and cause (lasting) tumour regressions [17]. The antibody is currently tested in phase III trials alone and in combination with IL-2 and vaccines. Another important development is sorafanib, a tyrosine kinase inhibitor, B-Raf inhibitor, with important anti-VEGFR2 mediated anti-angiogenic properties which is currently evaluated in combination with chemotherapy in phase III trials as first and second-line treatments [18]. The more complex, but of fundamental importance, is the ongoing research on how to utilise dendritic cells. Remarkable results have been reported by Rosenberg' s group with chemotherapy-lymphodepletion followed by adoptive transfer of autologous tumour-reactive lymphocytes in highly pretreated refractory melanoma patients. A response rate of 51% in 35 patients has been reported and should provide insight into what is crucial to obtain tumour regression in melanoma patients [19].

Conclusions

There is no effective therapy for metastatic melanoma. Polychemotherapy or chemoimmunotherapy have not demonstrated survival benefits. Vaccines have shown thus far very little activity in stage IV disease. New drugs can, and should be offered as first-line to intensify the quest to identify effective agents.

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