The Pathway Ahead in Melanoma Trials

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Reviewing treatment modalities for melanoma provides many sobering reminders that advances in our scientific understanding have not yet translated into meaningful clinical benefit. As clearly delineated by the authors, the “standard” treatment of dacarbazine chemotherapy has a poor response rate and lacks durability. A variety of other agents have been tested as single agents and numerous attempts have been made at combined chemotherapies, but in head-to-head trials with dacarbazine, no other approach has proven to result in superior overall survival. Thus, the dismal prognosis for metastatic disease remains largely unaffected by current treatments.

A variety of compounds in various stages of testing are showing promise. Many of these agents are based on greater scientific insight into the genetic changes involved in melanomagenesis and directly target key oncogenic pathways (reviewed by Miller and Mihm).[1] If these treatments are successful, the current therapeutic landscape will be altered, perhaps leading to personalized therapies based on particular aberrations in the individual patient’s tumor.

Cell-Cycle Checkpoint Control

A variety of familial and sporadic mutations in melanoma affect the cell-cycle apparatus. A small fraction of melanomas have a familial basis, and in a subset of these, lesions in the cell-cycle genes CDKN2A and CDK4 provide a molecular basis for this risk. The CDKN2A locus encodes the tumor suppressor INK4a that acts at the G1 checkpoint to arrest progress through the cell cycle. Its loss by deletion or mutation removes this brake. CDK4 functions to drive the cell cycle forward, is a target of INK4a activity, and when mutated, can no longer be suppressed by INK4a. Sporadic melanomas also develop mutations in this pathway through the acquisition of aberrations in CDK4 and its partner CDK6. These genes coordinate many different upstream signals and are a key component of the apparatus that determines whether or not a cell will divide.

Molecular restoration of INK4a tumor suppressor function lost through genetic mutation has proven to be a difficult therapeutic target. On the other hand, mutations in the CDK genes involve either amplifications of the respective genes or mutations that render them hyperactive. These changes are more amenable to pharmacologic therapy, as they may be mitigated by targeted inhibition of their activity. Several such compounds are under development, but early candidates such as flavopiridol and UCN-01 have performed poorly (reviewed by Sekulic et al).[2] Cell-cycle control remains an active area of drug development, and several preclinical molecules are being investigated (reviewed by Tse et al).[3]

Growth Factors

The inhibition of growth factor signaling is a successful approach in several other malignancies.[4] In melanomas, mutations of the downstream signaling molecule BRAF are found in about 70% of lesions,[5] and in mouse models BRAF mutation leads to increased nevi and the development of metastatic melanoma.[6] BRAF mutations constitutively activate this molecule, leading to pro-proliferative signaling through the MAP kinase pathway irrespective of activity of upstream growth factors. This promitotic stimulus appears essential for melanoma growth since disruption through RNAi leads to growth arrest and apoptosis.[7] In melanomas lacking BRAF mutation, constitutively activating mutations in NRAS are prevalent, and disruption by RNAi also leads to apoptosis.[8] Like BRAF mutation, NRAS mutation leads to activation of the MAP kinase pathway, providing a mechanistic basis for the observation that melanoma cells harbor either BRAF or NRAS mutation, but not both.[9] Melanoma appears to depend on MAP kinase activation for survival and...
develops mutations in either BRAF or NRAS to accomplish this. A variety of molecules in various stages of development target these pathways. NRAS requires post-translational myristoylation, and farnesyl transferase inhibitors are being tested as a way to block NRAS activity. A variety of inhibitors directed at BRAF are being explored, ranging from sorafenib (Nexavar), which has activity against a broad range of tyrosine kinases, to molecules in preclinical stages such as PLX4720 which has been developed as a molecule with high selectivity toward BRAF.[10] In tumors without activating BRAF or NRAS, upstream inhibition of growth factor receptor tyrosine kinases, such as IGF-1R,[11] c-Kit, and c-MET may also play a role, and inhibitors of these receptor tyrosine kinases are currently in clinical development.

**Tumor Vasculature/Angiogenesis**

Since the discovery that solid tumors utilize the angiogenic process to develop a vascular supply capable of sustaining continued tumor growth, numerous attempts have been made to exploit this dependence. The best studied angiogenic molecules are the VEGF family of growth factors and their associated receptors, which enable vessel growth through endothelial mitogenesis. Melanomas overexpress VEGF (reviewed by Streit and Detmar).[ 12] Melanoma cells treated with dacarbazine develop resistance that is associated with a more aggressive phenotype, which is partially attributed to VEGF expression.[13] In light of this, efforts to use agents directed against VEGF may increase the therapeutic effect of dacarbazine and decrease the ability of melanoma cells to establish metastatic lesions by preventing the development of a vascular supply. One such agent is bevacizumab (Avastin), a monoclonal antibody directed against VEGF. Since this therapeutic approach is not necessarily lethal to melanoma cells, trials are underway using bevacizumab in conjunction with other chemotherapies.[14]

Of note, sorafenib, which has activity against both VEGF signaling and BRAF, has been a source of excitement in the treatment of melanoma, as it is able to simultaneously block these two key pathways. In combination with dacarbazine, sorafenib doubles the response rate from 12% to 24%. However, our enthusiasm is blunted because the overall survival between dacarbazine and dacarbazine/ sorafenib recipients is no different and there is no evidence of benefit when sorafenib is combined with paclitaxel and carboplatin. The improved biologic understanding of melanoma is leading to a new generation of molecularly targeted therapeutics that provide much of the backbone for new clinical trials. As well summarized by Bhatia et al, many forms of chemomonotherapy are well tolerated, but are primarily palliative. High-dose IL-2 (Proleukin) works for a very small subset of patients, and it cannot be determined in advance who they might be. Current combination therapy does not increase survival and is less well tolerated.

As the authors conclude, the standard of care is participation in clinical trials. Here we have provided a very brief glimpse of some of the pathways that are mutated in melanoma and pharmacologic agents targeted toward those defects. These agents are becoming increasingly prevalent in clinical trial protocols. Some of these agents are directed toward particular mutations, suggesting that therapy may someday be personalized, to take into account the molecular profile of individual tumors.

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**References:**


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