Commentary (Mastrangelo/Berd): Systemic Treatments for Advanced Cutaneous Melanoma

November 01, 1995
By Michael J. Mastrangelo, MD [1] and David Berd, MD [2]

Anderson and colleagues present a comprehensive and factually accurate overview of systemic treatment for advanced melanoma. They correctly identify dacarbazine as the only single agent officially sanctioned for the treatment of metastatic melanoma. They further opine that "dacarbazine alone remains the standard of care for initial chemotherapy treatment of metastatic melanoma." With overall response rates of 10% to 20%, a complete response rate of less than 4%, and no evidence that treatment with dacarbazine improves survival over best palliative care, one questions whether or not dacarbazine would merit approval if reevaluated today.

In the constant quest for the much needed improvement in therapeutic efficacy over this pyrite standard, dacarbazine has been used in combination with one or more even less active agents. Some of these combinations have a pharmacologic basis and others, a pithy acronym (eg, BOLD). The consensus opinion, to which we once subscribed, is that the considerable increment in toxicity could not be justified on the basis of the modest improvement in objective response rates. However, data are now appearing, albeit from single-institution phase II trials, that indicate that some combination regimens are superior to dacarbazine alone. Anderson et al review the University of Texas M. D. Anderson Cancer Center experience integrating interferon-alfa and interleukin-2 (IL-2) with cisplatin, vinblastine, and dacarbazine (CVD). Overall response rates with various sequences of administration ranged from 63% to 73%, but median remission duration was brief (about 6 months). It is not clear why they neglected to mention the clinically significant complete response rate of 17% (27/155), which they presented in a previous report [1]. With a median follow-up to 30+ months, 16 (10%) of their patients remained disease-free.

The Dartmouth Regimen
In 1984 Del Prete et al [2] reported four complete and seven partial responses among 20 assessable patients treated with dacarbazine + carmustine (BCNU [BiCNU]) + cisplatin (Platinol) + tamoxifen, a regimen brandishing neither a pharmacologic rationale nor an acronym. We and others subsequently evaluated this so-called Dartmouth regimen. These data are reviewed by Anderson and colleagues. We have updated our own experience [3], which now includes 41 partial (28%) and 17 complete (12%) responses in 147 evaluable patients, for a 40% overall response rate (95% confidence interval, 32% to 48%). All sites except the CNS have responded. In addition to the anticipated hematologic and renal toxicity, 16 patients (11%) experienced nonfatal thromboembolic events. Increasing the tamoxifen dose to as much as 240 mg/d did not increase the antitumor response rates but did yield significantly more severe thrombocytopenia.

Which drugs constitute the essential components of this regimen continues to be debated. Rusthoven et al [4] have completed a well-designed, placebo-controlled trial in which 198 patients were randomized to receive either dacarbazine + BCNU + cisplatin or the same drugs plus tamoxifen (160 mg/d for 6 days as a loading regimen, followed by 40 mg/d for maintenance). The results of this scientifically rigorous trial seemingly challenged our data, as well as the results of others. Although the 21% response rate (6 complete and 14 partial responses) in the placebo group was similar to the combined Jefferson/Dartmouth experience of 18% in 39 patients, the addition of tamoxifen yielded only a 27% response rate (3 complete and 26 partial responses), and this increment was not statistically significant. This is in sharp contrast to the results obtained in multiple earlier phase II
trials. What is equally disturbing is that despite the equivalent dose intensity in both arms, tamoxifen did not increase hematologic toxicity or the incidence of deep vein thrombosis (3/101 with, 6/97 without). Further, few menopausal symptoms were noted in female patients. These observations suggest that tamoxifen was virtually without biologic impact. Perhaps the results of the North Central Oncology Group trial will clarify these important issues.

With an overall response rate of less than 50%, it seems reasonable to conclude that the median survival of Dartmouth regimen-treated patients is not superior to those patients only given best palliative care. Current wisdom dictates, therefore, that this regimen should not be considered an approved therapy for patients with metastatic melanoma. Indeed, partial responses are disappointingly short (median, 4 months). However, as with the M. D. Anderson regimen, complete remissions were quite durable (median, 20 months). More importantly, 7 of 17 patients remain in continuous unmaintained complete remission for 19 to 82 months, suggesting that this regimen may have curative potential.

Both Regimens Are Superior to Dacarbazine Alone

As with all chemotherapy, the response rates achieved are dependent on the patient population treated and the fidelity with which the treatment is administered. Whether the Dartmouth or M. D. Anderson regimen is more effective may be discernible in phase III testing, although unfortunately, even phase III trials can yield conflicting or misleading results. However, the available data strongly suggest that both regimens are superior to dacarbazine alone. Pending publication of the results of randomized trials, we consider the Dartmouth regimen to be first-line treatment for patients with metastatic melanoma and a gold standard against which other treatments should be measured. This recommendation is based on the occurrence of durable complete remissions, patient acceptance, and relative ease of administration as compared with IL-2 or interferon-containing regimens. Actually, the final judgment will be made in the marketplace. Practicing oncologists will not be denied a good, albeit officially unendorsed, treatment. Nor will they accept an inferior treatment no matter how prominent the endorsements.

References:


Links:
[1] [http://www.physicianspractice.com/authors/michael-j-mastrangelo-md](http://www.physicianspractice.com/authors/michael-j-mastrangelo-md)
[2] [http://www.physicianspractice.com/authors/david-berd-md](http://www.physicianspractice.com/authors/david-berd-md)