In their article in this issue of ONCOLOGY, Grotz et al outline the decision tree used at their institution to evaluate and treat patients with in-transit melanoma. Their algorithm begins, at a patient’s initial presentation, with a full-body positron-emission tomography (PET)–computed tomography (CT) scan for (re)-staging and, appropriately, consideration of clinical trial enrollment. Outside of a clinical trial, however, the simplest therapy—surgical excision—is the favored initial treatment of isolated lesions or small groups of in-transit/satellite lesions that can be excised completely. With regard to resection margins in this setting, it is generally accepted that the goal is simply a clear soft-tissue margin—or the largest margin that can be achieved without requiring a more complex closure. Also, in the setting of localized, completely resectable disease, sentinel lymph node biopsy can be considered in much the same way as for a primary lesion, regardless of whether the first draining basin has already been surgically cleared.

In patients in whom complete surgical resection is not feasible, it is important to take into account the number, distribution, and depth of in-transit lesions in order to select the most appropriate therapy. Patients with in-transit lesions not amenable to resection often have lesions that are quite variable in terms of size and depth. This variability mandates consideration of therapeutic combinations that work through one or more of the following mechanisms: mechanical destruction, immunologic, and/or cytotoxic.

According to the algorithm proposed by Grotz et al, pulsed dye laser (PDL) therapy, either alone or in combination with topical therapy, should be considered for superficial “pepper” lesions. In addition to PDL, CO2 laser ablation is another tool to keep in mind for cases in which local destructive therapy is indicated. CO2 laser ablation is widely available and has the advantage of being useful for dermal as well as deeper-seated lesions. The resultant small but multiple tissue defects can be allowed to heal by secondary intention.

Melanoma is well known to be a highly immunogenic tumor, and the presence of in-transit melanoma lesions presents a unique opportunity to utilize topical and/or intralvesional treatment strategies in an attempt to elicit a tumor-specific immune response; such a response can potentially impact subclinical disease before it declares itself, and in rare cases, systemic immunity can be elicited. Perhaps the first agent to be administered directly into melanoma lesions was bacille Calmette-Guérin (BCG). As reported by Morton et al in 1974, not only did intralvesional therapy with BCG elicit regression of a high percentage of injected lesions, but antitumor responses were seen in noninjected lesions as well.[1,2] It was hypothesized that intralvesional BCG acts as a local, autologous tumor vaccine. It has since been demonstrated that BCG is a toll-like receptor (TLR) agonist that can induce production of Th-1 cytokines and cause maturation of antigen-presenting cells; this demonstration adds support to the hypothesis of an immune-based mechanism of action.[3] From a practical standpoint, intralvesional therapy can be very useful in managing in-transit disease involving the head, neck, trunk and proximal extremities, where isolated limb perfusion/infusion is obviously not feasible. Other agents that have been applied intralvesionally include cytokines such as interferon alpha, interleukin (IL)-2, and granulocyte macrophage colony–stimulating factor. Imiquimod (Drug information on imiquimod) (Aldara) is a topical immune-response modifier and TLR-7 agonist that is approved for the treatment of superficial basal cell carcinoma and anogenital warts. Topical imiquimod and a retinoid cream were combined with intralvesional IL-2 in a recent, small study of 3 patients with a total of 6 cutaneous and subcutaneous melanoma metastases. Regression was
confirmed histopathologically in all treated tumors out to 27 months of follow-up.[4] In a study of 13 patients with multiple cutaneous and/or subcutaneous melanoma metastases, topical imiquimod followed by intralesional IL-2 resulted in an overall clinical response in 50.5% of the treated lesions, with 40.7% of the responses being complete.[5] Notably, most of the lesions that responded to the treatment were cutaneous (as opposed to subcutaneous), which is concordant with most reported experiences with intralesional therapy.

Although cytotoxic agents, including intralesional cisplatin (Drug information on cisplatin) and topical dinitrochlorobenzine, have been used for in-transit melanoma with some success in the past, these agents have fallen out of favor. Topical 5-FU was recently administered in an alternating fashion with topical imiquimod, resulting in a 42% complete response rate in patients with cutaneous melanoma metastases.[6] Recently another agent, Rose Bengal, has been shown to be directly cytotoxic to melanoma cells and also to have a potential immunologic mechanism of action. When Rose Bengal was given intralesionally, observed dose-dependent response rates of up to 69% were seen, and there was also a 44% response in noninjected “bystander” lesions.[7]

With a multitude of available therapeutic options, an algorithm such as the one presented by Grotz et al is important to keep in mind when attempting to devise a logical, individualized treatment for a given patient. For localized in-transit disease, less is more, with local destruction, excision, and intralesional therapy being the cornerstones of treatment. If local therapies fail or if distant disease arises, isolated limb perfusion and systemic therapy remain effective options.

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REFERENCES


