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New Agents Stir Interest in Intralesional Therapy for Cutaneous Metastatic Melanoma

Initial interest in intralesional therapy was stimulated decades ago when Mastrangelo et al. reported resolution of 17 injected and 47 uninjected intracutaneous metastatic melanoma tumors in a 77-year old male after injections of Bacille Calmette-Guérin (BCG) (Cancer. 1975 Oct; 36(4):1305-8). Interest waned, however, when disseminated BCG led to anaphylactic reactions and death in a subsequent trial, according to Merrick Ross, MD, MD Anderson Cancer Center, Houston, TX. Other agents and approaches in this population have included carbon dioxide lasers, cryotherapy, electrochemotherapy (electroporation) and cytokines (interleukin-2 and interferon-alpha and beta), Dr. Ross

said at the HemOnc Today Melanoma and Cutaneous Malignancies meeting in New York City. *IL-2, he noted, produced 70%-80% overall response rates and 62.5%-69% complete responses, but was time-intensive, costly and did not demonstrate regression of non-injected lesions.*

Recently, interest in intralesional therapies has been aroused by three promising agents that are locally ablative and systemically active: Allovectin, ONcoVEX, PV-10 (Rose Bengal), Dr. Ross said.

Candidates for intralesional therapy include patients with unresectable, multiple or advanced locally/regionally metastatic Stage IIIb/c or Stage IV M1a melanoma, regardless of distant disease. Tumors must be accessible for direct injection. The population represents 2.3-6.5% of patients with primary melanomas, and includes high-risk groups with thick or ulcerated lesions, positive sentinel lymph nodes, and lower extremity tumors. These patients have significant morbidity, and risk for distant disease and death is >50%.

"These agents," Dr. Ross said in an interview, "have heightened interest into a field that people have become kind of 'ho-hum' about. Some of the data are relatively compelling and there's special interest with regard to patients with comorbidities who can't tolerate other aggressive therapies –for example elderly patients who can't tolerate any level of toxicity, which these drugs rarely have."

Allovectin-7 is an HLA-B7/beta2microglobulin plasmid formulated with cationic lipids. Potential mechanisms of action include induction of allogeneic responses against HLA-B-27, upregulation/restoration of major histocompatibility complex molecules and induction of proinflamatory response by pDNA/lipid complex. In a Phase II trial of 133 patients, the overall response rate was 12% with no grade 3 or higher toxicities. A Phase III trial is ongoing.

OncoVEX$^{GM\text{-}CSF}$, an oncolytic *Herpes simplex* virus encoding GM-CSF, is thought to work by replicating only in tumor cells and lysing injected tumors. Lysed cells are then taken up by antigen presenting cells. An adaptive antimelanoma response enhanced by local expression of GM-CSF may also occur. In a phase II trial, the objective response rate was 28%, with regression of injected and non-injected lesions. A Phase III trial is ongoing.

PV-10, a sterile, non-pyrogenic solution of Rose Bengal (RB) disodium (10%), is a small molecule fluorescein derivative that has been used as a hepatic (^{131}I radiolabeled RB, Robengatope) and topical ophthalmic diagnostic (Rosettes and Minims). PV-10 accumulates only in lysosomes of cancer cells, elicting acute autophagy within 30-60 minutes. The bystander effect is thought to occur when antigenic tumor fragments are exposed acutely to antigen-presenting cells.

In Phase II testing among 80 subjects with Stage III/IV melanoma at 7 Australian and US centers, locoregional control (complete response + partial response + stable disease) was reported in 71% of patients and in 55% of bystander lesions. Complete response rates were 24% in both target and bystander lesions. Bystander responses correlated highly with positive objective responses in the target lesions. No grade 4 or 5 adverse events were reported. A Phase III trial of PV-10 is being designed.

Dr. Ross commented that trials of novel combinations, for example of PV-10 injections for bulky disease followed by external beam radiotherapy (Foote et al., *Mel Res* 2009), or high-dose intralesional IL-2 with topical imiquimod and retinoid cream (Shirakawa et al., *Mel Res* 2011) may be followed by combinations with new targeted BRAF agents or with anti-CTLA-4 agents or PD (programmed death)-1. ❑