

Intralesional therapy for metastatic melanoma with a focus on PV-10



Sanjiv S Agarwala*

“A resurgence of interest in intralesional therapy, due to the recent development of agents appear to not only ablate tumors locally, but produce confirmed systemic effects in animal models and the clinic.”



A significant fraction of patients with melanoma have locally advanced and regional disease that is not curable by standard surgical resection. Various therapeutic modalities have been attempted for such patients including re-resection, radiation therapy and regional perfusion with chemotherapeutic agents. The toxicity of systemic agents has been a deterrent to the use of aggressive systemic therapy in these patients; furthermore, many patients are elderly and have comorbidities that preclude their use. This has made intralesional therapy an attractive proposition for some of them; in general, patients with unresectable stage IIIB/c or stage IV M1a melanoma who have tumors accessible for direct injection are potential candidates for intralesional therapy.

Intralesional therapy for metastatic melanoma has been ‘around’ since the 1970s when Bacille Calmette–Guérin was first reported to produce remission in injected lesions and also distant metastases [1]. An immune-mediated systemic response was hypothesized to be the basis behind the occasional systemic response but randomized trials of Bacille Calmette–Guérin have failed to confirm a significant clinical benefit and this approach is no longer used in practice [2].

A resurgence of interest in intralesional therapy due to the recent development of agents

appear to not only ablate tumors locally, but produce confirmed systemic effects in animal models and the clinic. Allovectin-7®, OncoVEX^{GM-CSF} and PV-10 are three such investigational agents that are in various stages of clinical development.

Allovectin-7 is a plasmid–lipid complex with the DNA sequences encoding HLA-B7 and $\beta 2$ microglobulin, both components of MHC-I. A lack of or reduced expression of MHC-I in melanoma cells is one mechanism by which these cells evade recognition by the immune system. Allovectin-7 induces a fivefold increase in the frequency of HLA-B27 cytotoxic T cells, upregulates or restores MHC-I molecules, and induces a proinflammatory response.

In a Phase II trial of Allovectin-7 that included 133 patients with stage IIIB/c and IV M1a/b melanoma, the overall response rate (ORR) was 12% and toxicity was mild [3]. A Phase III trial of Allovectin-7 compared with chemotherapy with dacarbazine (DTIC)/temozolomide in recurrent stage III or IV melanoma has completed accrual and results are expected in 2012.

OncoVEX^{GM-CSF} is an oncolytic *herpes simplex* virus encoding granulocyte-macrophage colony stimulating factor (GM-CSF). Its mechanism of action is based upon its ability to replicate only in tumor cells, causing lysis. Lysed cells are then

*Oncology & Hematology, St Luke's Hospital & Health Network, 801 Ostrum Street, PA, USA; agarwas@slhn.org

"It remains to be seen whether intralesional therapy with any of the above agents will be proven to be beneficial in randomized trials."

taken up by antigen-presenting cells and local expression of GM-CSF adds to the activity. A Phase II trial of OncoVEX^{GM-CSF} was recently reported showing a 28% ORR (20% complete) and some of these were durable [4]. Occasional responses were observed in uninjected visceral lesions as well. A Phase III trial has recently completed enrollment of 360 stage IIIb/IV melanoma patients randomized to a ratio of 2:1 to OncoVEX^{GM-CSF} versus subcutaneous GM-CSF alone. The end points are durable response at 6 months and overall survival.

PV-10 is a small molecule fluorescein derivative. It is a nonpyrogenic solution of Rose Bengal disodium (10% RB), which is not metabolized, has approximately a 30-min circulatory half-life and is excreted via the biliary system. PV-10 is selectively taken up by the plasmalemma of cancer cells and accumulates in the lysosomes [5], triggering lysosomal release leading to autolysis within 30–60 min. Antigenic tumor fragments being taken up by antigen-presenting cells is believed to be the mechanism behind the systemic 'bystander' effect in uninjected tumors.

Following promising Phase I results [6], a multicenter, international Phase II trial, in 80 patients with measurable stage III–IV melanoma, was conducted at multiple centers in the USA and Australia. Intralesional injections of PV-10 were administered to up to ten target and up to ten nontarget cutaneous, subcutaneous or nodal lesions. New or incompletely responsive lesions were retreated at weeks 8, 12 or 16, with follow-up at 52 weeks. Target lesions were ≥ 0.2 cm in diameter, with at least one confirmed by biopsy. Investigators observed up to one to two untreated, biopsy-confirmed bystander lesions that were typically small or difficult to access (including visceral lesions). The primary end point was objective response rate for injected lesions.

Among the subjects treated (49 male:31 female; median age: 70 years [range: 33–97 years]), the median number of PV-10 treatments was two (range: 1–4), with a median dose per treatment of 1.6 ml (0.1–15). Twenty four percent of patients had complete responses (CR) in target lesions and 25% had partial responses for an ORR of 49%. The locoregional disease control (CR plus partial response plus stable disease) rate was 71%. Among subjects with bystander lesions, CR of their untreated lesions was reported in 24%, ORR in 37% and locoregional

control in 55%. Regression of bystander lesions strongly correlated with response in target lesions.

In an updated analysis of the first 40 patients [7], those with CRs achieved significantly longer progression-free survival (11.1 months) than those with stable disease or progressive disease (2.8 and 2.7 months, respectively). Responses in injected lesions appeared to be unrelated to disease stage or prior treatment. No grade 4 or 5 adverse events were attributed to PV-10, and overall, adverse events were locoregional and predominantly mild-to-moderate.

A Phase III trial is in development with the intention of enrolling approximately 300 subjects with stage IIIb–IV (M1a) melanoma to compare PV-10 with a control arm of chemotherapy with either dacarbazine or temozolomide, with progression-free survival as a primary end point. Enrollment in the 30-month trial is scheduled to begin in early 2012.

The year 2011 has been a good one for melanoma research and two new drugs, ipilimumab, an anti-CTLA-4 antibody and a targeted agent, and vemurafenib, a highly selective inhibitor of BRAF, a mutation found in approximately 50% of melanomas, have both been approved by the US FDA. The potential for them to be combined with a successful intralesional therapy with nonoverlapping toxicity and mechanism of action is obvious.

It remains to be seen whether intralesional therapy with any of the above agents will be proven to be beneficial in randomized trials. If shown to be effective, they will add another weapon to the rapidly expanding arsenal for melanoma. Their ease of administration by local injection, low toxicity and applicability to sicker patients who are not candidates for aggressive systemic therapy make them attractive candidates for development. We look forward to 2012 with great anticipation.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- 1 Mastrangelo MJ, Bellet RE, Berkelhammer J *et al.* Regression of pulmonary metastatic disease associated with intralesional BCG therapy of intracutaneous melanoma metastases. *Cancer* 36, 1305–1308 (1975).
- 2 Agarwala SS, Neuberg D, Park Y, Kirkwood JM. Mature results of a Phase III randomized trial of Bacillus Calmette–Guerin (BCG) versus observation and BCG plus dacarbazine versus BCG in the adjuvant therapy of American Joint Committee on Cancer stage I–III melanoma (E1673). *Cancer* 100(8), 1692–1698 (2004).
- 3 Bedikian AY, Richards J, Kharkevitch D, Atkins MB, Whitman E, Gonzalez R. A Phase 2 study of high-dose Allovectin-7 in patients with advanced metastatic melanoma. *Melanoma Res.* 20(3), 218–226 (2010).
- 4 Kaufman HL, Kim DW, DeRaffele G, Mitcham J, Coffin RS, Kim-Schulze S. Local and distant immunity induced by intralesional vaccination with an oncolytic herpes virus encoding GM-CSF in patients with stage IIIc and IV melanoma. *Ann. Surg. Oncol.* 17(3), 718–730 (2010).
- 5 Wachter E, Dees C, Harkins J, Fisher W, Scott T. Imaging photosensitizer distribution and pharmacology using multiphoton microscopy. *Proc. SPIE* 4622, 112–118 (2002).
- 6 Thompson JF, Hersey P, Wachter E. Chemoablation of metastatic melanoma using intralesional Rose Bengal. *Melanoma Res.* 18(6), 405–411 (2008).
- 7 Agarwala AA, Thompson JF, Smithers BM *et al.* Chemoablation of metastatic melanoma with PV-10. Presented at: 7th International Melanoma Congress. Sydney, Australia, 4–7 November 2010.