Intralesional Therapy for In-transit and Satellite Metastases in Melanoma

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KEYWORDS

• Intralesional therapy • Bacille Calmette-Guerin • Vaccinia • Scarification
• Granulocyte-macrophage colony-stimulating factor • Rose bengal • Melanoma
• In-transit disease

KEY POINTS

- Agents such as bacille Calmette-Guerin, interleukin-2, interferon, rose bengal, and granulocyte-macrophage colony-stimulating factor/viral recombinants are viable options for treatment of local-regional dermal and subcutaneous melanoma metastases through intralesional injections.
- Remission rates are significantly higher than when they are used systemically to treat metastatic disease, suggesting that the concentration of the agent within the tumor is a significant factor in determining response.
- The mechanism of the antitumor effect is postulated to be immunologic but a bystander effect caused by the inflammatory response is also possible.

INTRODUCTION

Intratumoral therapy with bacteria/bacterial products dates to at least the 1890s.[1] It was in 1893 that William Coley published his case series of the deliberate infection of sarcomas with a mixture of *Streptococcus pyogenes* and *Serratia marcescens*. He concluded that bacterial infection could induce tumor regression. A scientific basis for this claim was provided by Zbar and Rapp[2] who showed regression of subcutaneous implants of a diethyl-nitrosamine–induced hepatocellular carcinoma in inbred strain-2 male guinea pigs by intratumor injection of bacille Calmette-Guerin (BCG) with regression not only of the injected tumor but also regression of regional nodal

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metastases. The animals were resistant to rechallenge with the same tumor.[2] This finding sparked renewed interest in intratumoral therapy as an approach not only to local tumor regression but also to inducing systemic antitumor immunity.

Over the ensuing decades, intratumoral therapy has expanded beyond the use of microbes and microbial products (eg, BCG, methanol extraction residue of BCG, purified protein derivative of *Mycobacterium tuberculosis*, vaccinia, *Clostridium novyi* NT [no toxin]) to chemicals (eg, dinitrochlorobenzene, rose bengal), cancer chemotherapeutic agents (eg, nitrogen mustard, 5-fluorouracil, imiquimod), cytokines (eg, interferon, interleukin-2 [IL-2], granulocyte-macrophage colony-stimulating factor [GM-CSF]), recombinant organisms (eg, vaccinia/GM-CSF, herpes simplex/GM-CSF, fowlpox/tumor antigen), and hybrid molecules (eg, mesothelin-diphtheria toxin gene). This list is incomplete and is being added to on a regular basis.

The obvious appeal of the intratumoral (intralesional/topical) approach to therapy is the ability to deliver a high concentration of the therapeutic agent directly to the tumor, usually with minimal systemic effects. The clinical experience in melanoma with the most extensively studied agents is reviewed in this article. Although regression of systemic disease has been more elusive, locoregional response rates approach 90%. We have found this approach invaluable in the treatment of dermal satellite and in-transit metastases, particularly those in cosmetically or functionally eloquent areas and also when the lesions encompass a large area defying surgical excision. This treatment can also be applicable in frail or medically compromised patients. To encourage more widespread application, this article provides detailed instructions on the use of some commercially available agents, such as BCG and the cytokines.

VACCINIA

Vaccinia is a large poxvirus with a double-stranded DNA genome that closely resembles cowpox. It is the active constituent of the vaccine that eradicated smallpox. Vaccination has been discontinued and thus a large segment of the population is unprotected. Because of bioterrorism concerns, the vaccine is sequestered and no longer available for clinical use. Use in cancer treatment was prompted by its oncolytic nature and the ability of the virus to activate macrophages, professional antigen-presenting cells. This ability in turn could enhance systemic immunity. Vaccinia virus has been used for intralesional therapy for cutaneous melanoma.

In 1961, Belisario and Milton[3] reported treating a 29-year-old woman with extensive in-transit deposits of melanoma with vaccinia virus intralesionally. All injected lesions resolved or decreased in size. Their work continued into the 1970s, studying both intralesional vaccinia and systemic immunization. Everall and colleagues[4] reported a series of 48 patients with primary melanomas who were randomized to having the primary lesion injected with vaccinia 2 weeks before excision versus primary excision alone. Relapse-free survival was improved in the patients treated with vaccinia.

In anticipation of using vaccinia as a vector, Mastrangelo and colleagues[5] treated 5 patients with metastatic melanoma accessible to injection with intralesional therapy with the wild-type vaccinia. All patients developed antivaccinia antibody titers. Despite this, infectivity could be maintained with repeat treatments. The injections were well tolerated. There were 1 complete (10+ years' duration) and 3 partial remissions. However, this product is no longer available.

BACILLE CALMETTE-GUERIN

BCG is prepared from an attenuated strain of *Mycobacterium bovis*. It is similar enough to its wild ancestors to provide immunity against *M tuberculosis* (its original