Cancer Immunol Immunother (2014) 63:1231–1232
DOI 10.1007/s00262-014-1584-1

LETTER TO THE EDITORS

# Limited efficacy of intratumoral IL-2 applied to large melanoma metastases

**Benjamin Weide · Thomas Kurt Eigentler · Giuliano Elia · Dario Neri · Claus Garbe**

Received: 26 May 2014 / Accepted: 5 July 2014 / Published online: 24 July 2014


Dear Editors,

Moreno-Ramirez et al. describe the case of a female patient with two bulky in-transit metastases treated with 6–10 MIU intratumoral interleukin 2 (IL-2). The lesions progressed rapidly during 4 weeks of treatment and new lesions occurred. The patient died 2 weeks later because of a severe metabolic disturbance as paraneoplastic syndrome. The authors concluded that intralesional IL-2 should be offered cautiously in patients with bulky in-transit melanoma metastases.

In response to this report published in the current issue, we want to point out that rapid disease progression during intralesional therapy considered to be related to IL-2 was not observed in our prior studies. In contrast, favorable long-term outcome and high response rates upon subsequent chemotherapies were observed in IL-2-treated patients [1, 2]. Nevertheless, according to our experience using free IL-2, efficacy of therapy is indeed lower in larger metastases, although not analyzed systematically in our prior clinical trials [3]. Even if the dose per lesion can be increased, longer treatment durations up to several months were necessary to achieve clinical responses [3, 4]. We recommended increased doses of 6 MIU per individual lesions larger than 2 cm [3, 4].

IL-2 has different known dose dependent, in part opposite effects, like expansion of regulatory T cells and induction of their suppressive characteristics or on the other hand activation of cellular antitumor immunity [5]. Therefore, we assume that a high concentration of IL-2 at a tumor tissue is crucial for efficacy. These high concentrations can only insufficiently be reached through systemic therapy, with its dose-limiting toxicity [6] or by low doses of IL-2 injected in large metastases.

Therefore and in contrast to our initial recommendations, we currently restrict intratumoral therapy with free IL-2 to lesions up to 1 cm in longest diameter and increase the dose per lesion as tolerated up to a maximum of 18 MIU units IL-2 per day. Recurrences developing during therapy should be included in subsequent treatments as soon as these become evident. In contrast, the applied dose in the patient presented by Moreno-Ramirez et al. with 6–10 MIU IL-2 applied on two bulky lesions, each with ~5 cm diameter, seems low.

Recently, the use of an antibody-based targeted version of IL-2 has exhibited promising anticancer effects in patients with stage IIIC melanoma. The use of the L19–IL2 fusion protein has allowed us to reduce the number of injections and is accompanied by favorable time-to-stage IV profiles [2]. Using this dataset, we now analyzed the rate of complete responses according to longest diameter of the lesion (Table 1). Promising complete responses were likewise observed in lesions larger than 1 cm, but due to the low number of large lesions in this trial, it is not clear whether the targeted form of IL-2 offers an advantage over free IL-2 for treatment of larger lesions.

If patients present several metastases of different diameters at baseline, a combined strategy, including initial

This reply refers to the comment available at doi:10.1007/s00262-014-1583-2.

B. Weide (✉) · T. K. Eigentler · C. Garbe
Department of Dermatology, University Medical Center, Liebermeisterstrasse 25, 72076 Tübingen, Germany
e-mail: Benjamin.weide@med.uni-tuebingen.de

G. Elia
Philochem AG, Otelfingen, Switzerland

D. Neri
ETH Zurich, Zurich, Switzerland

**Table 1** Complete responses of metastases individually treated with L19–IL2 [2]

| | $x < 5$ mm ($n = 451$) | 5 mm $< x <$ 10 mm ($n = 53$) | $x > 10$ mm ($n = 10$) |
|---|---|---|---|
| CR | 205 (45.4 %) | 24 (45.3 %) | 4 (40 %) |
| Non-CR | 246 (54.6 %) | 29 (54.7 %) | 6 (60 %) |

*CR* complete response

surgery of larger lesions followed by intralesional IL-2 applied to smaller lesions, is an option. In case of large single lesions, tumor debulking followed by intralesional IL-2 in case of incomplete resection might also be considered in addition to other treatment modalities like electrochemotherapy.

Another option for large lesions may arise by the combined application of different cytokines. Preclinical studies have shown that the combination of two antibody–cytokine fusion proteins (e.g., L19–IL2 plus L19–TNF) is associated with a more potent anticancer effect in a number of syngeneic immunocompetent mouse models of cancer [7]. Indeed, emerging results from a clinical study with L19–IL2 plus L19–TNF in patients with in-transit melanoma metastases have allowed the treatment of patients with bulky lesions, including a patient with a lesion of 13-cm diameter [Riccardo Danielli and Michele Maio, personal communication and manuscript in preparation]. Thus, it appears that the treatment of patients with bulky lesions may be best approached in the future either by the administration of high doses of L19–IL2 or by combinations of cytokines.

**Conflict of interest** G. Elia is employed by the Philogen group. D. Neri is a co-founder and shareholder of Philogen, the biotech company that has licensed the L19–IL2 antibody from the ETH Zurich. B. Weide and T. Eigentler received compensation from the Philogen group for advisory services. C. Garbe received compensation from the Philogen group for advisory services, for patient treatment and in his role as coordinating investigator of clinical trials.

## References


1. Weide B, Eigentler TK, Pflugfelder A, Leiter U, Meier F, Bauer J, Schmidt D, Radny P, Pfohler C, Garbe C (2011) Survival after intratumoral interleukin-2 treatment of 72 melanoma patients and response upon the first chemotherapy during follow-up. Cancer Immunol Immunother 60(4):487–493. doi:10.1007/s00262-010-0957-3
2. Weide B, Eigentler TK, Pflugfelder A, Zelba H, Martens A, Pawelec G, Giovannoni L, Ruffini PA, Elia G, Neri D, Gutzmer R, Becker JC, Garbe C (2014) Intralesional treatment of Stage III metastatic melanoma patients with L19-IL2 results in sustained clinical and systemic immunological responses. Cancer Immunol Res. doi:10.1158/2326-6066.cir-13-0206
3. Weide B, Derhovanessian E, Pflugfelder A, Eigentler TK, Radny P, Zelba H, Pfohler C, Pawelec G, Garbe C (2010) High response rate after intratumoral treatment with interleukin-2: results from a phase 2 study in 51 patients with metastasized melanoma. Cancer 116(17):4139–4146. doi:10.1002/cncr.25156
4. Radny P, Caroli UM, Bauer J, Paul T, Schlegel C, Eigentler TK, Weide B, Schwarz M, Garbe C (2003) Phase II trial of intralesional therapy with interleukin-2 in soft-tissue melanoma metastases. Br J Cancer 89(9):1620–1626. doi:10.1038/sj.bjc.6601320
5. Antony PA, Restifo NP (2005) CD4+ CD25+ T regulatory cells, immunotherapy of cancer, and interleukin-2. J Immunother 28(2):120–128
6. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, Abrams J, Sznol M, Parkinson D, Hawkins M, Paradise C, Kunkel L, Rosenberg SA (1999) High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 17(7):2105–2116
7. Schwager K, Hemmerle T, Aebischer D, Neri D (2013) The immunocytokine L19-IL2 eradicates cancer when used in combination with CTLA-4 blockade or with L19-TNF. J Invest Dermatol 133(3):751–758. doi:10.1038/jid.2012.376