Ann Surg Oncol (2019) 26:2495–2496
https://doi.org/10.1245/s10434-019-07435-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ASO AUTHOR REFLECTIONS

ASO Author Reflections: International Experience of Isolated Limb Infusion for Melanoma Shows Durable Response

John T. Miura, MD[1], Hidde M. Kroon, MD, PhD[2,3], and Jonathan S. Zager, MD, FACS[1]

[1]Department of Cutaneous Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL; [2]Department of Surgery, Royal Adelaide Hospital, University of Adelaide, Adelaide, SA, Australia; [3]Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia

PAST

Historically, managing patients with locoregionally metastatic melanoma confined to a limb was challenging due to the paucity of effective treatment options available. Isolated limb perfusion (ILP) and, since its introduction in 1992, isolated limb infusion (ILI) continue to be effective treatment modalities available for such patients. The advantages of ILI over ILP include its minimally invasive approach, lower complexity, and reduced overall morbidity. With the introduction of effective immunotherapy and numerous local (intralesional) therapies, the treatment paradigm for patients with in-transit disease continues to evolve, making it paramount to establish the efficacy of ILI to evaluate its place and relevance in the treatment of locoregionally metastatic limb melanoma. Previous large ILI series have reported favorable overall response rates (ORRs) ranging from 43 to 84%, with complete response (CR) rates ranging from 26 to 38%; however, its effect on long-term oncologic outcomes remains poorly defined.[1,2]

PRESENT

With the introduction of effective immunotherapy and new local (intralesional) treatments, the therapeutic options for locoregionally metastatic melanoma are ever-expanding.[3] Given this range of available options, appropriate therapy selection is an important area of research. Despite being around for three decades, ILI has not garnered similar enthusiasm as some newer agents, despite the fact that ILI has repeatedly demonstrated higher ORRs. In the present study conducted at nine international melanoma expert centers,[4] 687 ILIs were performed, resulting in minimal regional and no systemic toxicity, with a 64.1% ORR and a CR of 28.9%. Importantly, a CR was associated with an overall survival of > 6 years, highlighting the durability of a favorable response. Conversely, when immunotherapy is used as a singular agent, response rates are lower, while it is associated with significantly higher toxicity and, most importantly, potentially life-altering systemic adverse effects.[5] Therefore, even in the era of expanding immunotherapy, ILI remains a viable and important option for patients with in-transit limb melanoma.

FUTURE

The expansion of new treatments for locoregionally metastatic melanoma has invoked new questions germane to its clinical management. In view of this, a future challenge will be to preserve therapeutic relevance of ILI and augment its efficacy. The current study[4] clearly shows that a subgroup of patients harbor tumor biology that is responsive to ILI, resulting in durable responses. Therefore, a future aim will be to identify those who will respond to regional therapy, for instance by using tumor gene expression profiling, allowing clinicians to direct ILI to those who are likely to benefit from it, while offering other

ASO Author Reflections is a brief invited commentary on the article "Long–Term Oncologic Outcomes After Isolated Limb Infusion for Locoregionally Metastatic Melanoma: An International Multicenter Analysis". Ann Surg Oncol. Epub 25 Mar 2019. https://doi.org/10.1245/s10434-019-07288-w.

John T. Miura and Hidde M. Kroon contributed equally to this work.

First Received: 1 May 2019;
Published Online: 13 May 2019

J. S. Zager, MD, FACS
e-mail: Jonathan.Zager@moffitt.org

treatment modalities or combination treatments to those unlikely to respond to ILI. Other potential future aims are combination strategies, such as combining ILI with systemic immunotherapy, as demonstrated by Ariyan et al.[6] Finally, the ILI platform can be used to deliver novel agents regionally with tumor that is available for pre-, intra-, and postoperative biopsies to identify treatment-related changes.

DISCLOSURE John T. Miura, Hidde M. Kroon, and Jonathan S. Zager have no conflicts of interest to disclose.

REFERENCES

1. O'Donoghue C, Perez MC, Mullinax JE, et al. Isolated limb infusion: a single-center experience with over 200 infusions. *Ann Surg Oncol*. 2017;24:3842–3849.
2. Kroon HM, Coventry BJ, Giles MH, et al. Australian multicenter study of isolated limb infusion for melanoma. *Ann Surg Oncol*. 2016;23:1096–103.
3. Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol*. 2015;33:2780–8.
4. Miura JT, Kroon HM, Beasley GM, et al. Long–term oncologic outcomes after isolated limb infusion for locoregionally metastatic melanoma: an international multicenter analysis. *Ann Surg Oncol*. 2019. https://doi.org/10.1245/s10434-019-07288-w.
5. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373:23–34.
6. Ariyan CE, Brady MS, Siegelbaum RH, et al. Robust antitumor responses result from local chemotherapy and CTLA-4 blockade. *Cancer Immunol Res*. 2018;6:189–200.