Editorial Commentary

Prolonged disease control with local treatments in oligo-acquired resistance to immune-checkpoint inhibitors

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During the last years, immune-checkpoint inhibitors (ICIs) have been positioned as frontline treatment options for many tumor types. However, probably because of their rapid incorporation into clinical practice, many aspects regarding the intrinsic characteristics of these drugs and their effects are still unknown.

With their recently published paper, Schoenfeld *et al.* (1) addressed oligo-acquired resistance (oligoAR) in a cohort of 1,536 lung cancer patients treated with ICI at the Memorial Sloan Kettering Cancer Center. It is a clinical situation frequently faced by oncologists worldwide, and even though it is managed with different therapeutic strategies there is limited evidence to support them.

Up to date, a modest number of prospective studies have explored the potential benefit of local treatment of oligometastatic disease, although there is some variability in its definition on disease between trials. In patients with oligometastatic disease treated with chemotherapy, consolidation treatment with radiotherapy or surgery improves progression-free survival (PFS) and even overall survival (OS) (2-4).

Oligoprogressive disease is a slightly different clinical context, as it implies the assumption of an initial responsiveness to the systemic treatment, thus with a prognosis more favourable. Regarding local ablation of progressive lesions in patients receiving tyrosine-kinase inhibitors (TKIs) for mutation-driven tumors, it can allow the continuation of the treatment with the same drug beyond progression, although the vast majority of patients ultimately present polytopic disease progression (5-7).

Interestingly, the work by Schoenfeld *et al.* showed that those patients presenting oligoAR to ICI and treated with local therapy achieved a longer and greater benefit, with 58% without progression at last follow-up and 23.2% of patients maintaining disease control 2 years after the initial progression. Among the patients who received local treatment for oligoAR, 82% were treated with radiotherapy, 16% with surgical resection and 2% with radioembolization. It should be taken into account that in this study only patients treated with ICI monotherapy and not chemoimmunotherapy were included, and also required that all patients had registered a previous partial response to the treatment (1). Anyhow the results of this study are of high relevance and strongly support the local control of progressive disease when feasible, even though additional studies are required to stablish the optimal local therapy

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depending on the location of the lesions.

Reasons explaining this apparently greater efficacy of the local therapy in patients receiving ICI compared with patients receiving treatment with chemotherapy or TKIs might be key for a better understanding of the mechanism of action of immunotherapy. The most obvious explanation is that, as tumor antigens of the resistant clones are released after treatment with radiotherapy, these might be captured by antigen presenting cells (APCs) and presented to T lymphocytes (TLs), thus granting the control of tumor cells already present in the systemic circulation that could induce relapse in patients receiving other treatments. This would be in agreement with the abscopal effect, an immune-mediated radiological response in distant non-irradiated lesions observed after the administration of radiotherapy that is still under scientific debate (8), but on the other hand would recommend against surgical approach of oligoAR. However, further work is necessary to confirm this hypothesis, which might also imply that resistance to ICI is more dependent on changes of the tumor cells than on the immunosuppressive activity of the tumor microenvironment (TME).

This article also found differences in survival when comparing patients having one to three progressive lesions compared with those with four or more progressive lesions. Besides supporting a threshold of only three lesions to propose local treatment for patients with advanced disease receiving ICI, slightly lower than previous reports of oligoprogression with TKIs (5,7,9), it strongly suggests that oligoAR disease is a distinct entity with particular characteristics that deserves an individualized approach.

Although other different biological explanations for oligoAR have been proposed, an individual evaluation of every progressive lesion would be necessary to confirm the specific process in each case, with the additional complexity that mutual exclusivity is not mandatory.

Low bioavailability of the drug in certain tissues can favor the emergence of new lesions, which has been described for central nervous metastases in patients receiving first-generation of TKIs against epithelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) because of a lack of permeability of these drugs through the hemato-encephalic barrier (HEB) (7). With regard to ICI, the TME can impair antitumor efficacy both by preventing the access of the drug and by blocking immune cell infiltration (10).

Clonal heterogeneity is another main mechanism that has been associated with oligoAR, including not only DNA mutations but also epigenetic modifications that might abrogate antitumor T cell activities. Cell heterogeneity can be pre-existing because of different genetic mutations, and oligoAR would be the consequence of clonal selection of cells refractory to the immune system. Cell plasticity induced by epigenetic changes or other modifications might also favor this phenomenon (11).

Finally, the definition of oligoAR disease itself does not lack of complexity. The most sensitive imaging techniques, i.e., magnetic resonance (MR) or positron emission tomography (PET), are not routinely used for response evaluation, and some patients with widespread progressive disease might be incorrectly classified as oligoprogression. RECIST criteria 1.1 or even immune-related RECIST (irRECIST) do not take into consideration the behavior of individual lesions but the net changes in the sum of the diameters of target lesions (12). Additionally, new patterns of response to immunotherapy as pseudoprogression might act as a relevant confounding factor (13). At the end, what we are facing is the uncertainty of using radiological criteria to define a biological behaviour.

Considering all the above, if we understand oligoprogressive disease as a specific clinical outcome with distinct biological characteristics, other techniques as circulating tumor DNA (ctDNA) quantification or sequencing, as well as liquid biopsy, might be key for the diagnosis.

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References

1. Schoenfeld AJ, Rizvi HA, Memon D, et al. Systemic and Oligo-Acquired Resistance to PD-(L)1 Blockade in Lung Cancer. Clin Cancer Res 2022;28:3797-803.
2. Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol 2019;37:1558-65.
3. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol 2018;4:e173501.
4. Palma DA, Olson R, Harrow S, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. J Clin Oncol 2020;38:2830-8.
5. Gan GN, Weickhardt AJ, Scheier B, et al. Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. Int J Radiat Oncol Biol Phys 2014;88:892-8.
6. Ni Y, Liu B, Ye X, et al. Local Thermal Ablation with Continuous EGFR Tyrosine Kinase Inhibitors for EGFR-Mutant Non-small Cell Lung Cancers that Developed Extra-Central Nervous System (CNS) Oligoprogressive Disease. Cardiovasc Intervent Radiol 2019;42:693-9.
7. Weickhardt AJ, Scheier B, Burke JM, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. J Thorac Oncol 2012;7:1807-14.
8. Ngwa W, Irabor OC, Schoenfeld JD, et al. Using immunotherapy to boost the abscopal effect. Nat Rev Cancer 2018;18:313-22.
9. Xu Q, Liu H, Meng S, et al. First-line continual EGFR-TKI plus local ablative therapy demonstrated survival benefit in EGFR-mutant NSCLC patients with oligoprogressive disease. J Cancer 2019;10:522-9.
10. Hirata E, Girotti MR, Viros A, et al. Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin β1/FAK signaling. Cancer Cell 2015;27:574-88.
11. McGranahan N, Swanton C. Clonal Heterogeneity and Tumor Evolution: Past, Present, and the Future. Cell 2017;168:613-28.
12. Park HJ, Kim GH, Kim KW, et al. Comparison of RECIST 1.1 and iRECIST in Patients Treated with Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. Cancers (Basel) 2021;13:120.
13. Jia W, Gao Q, Han A, et al. The potential mechanism, recognition and clinical significance of tumor pseudoprogression after immunotherapy. Cancer Biol Med 2019;16:655-70.

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