Editorial

An innovative mesothelioma treatment based on miR-16 mimic loaded EGFR targeted minicells (TargomiRs)

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Introduction

On September 2017, *The Lancet Oncology* published the safety and activity data of a first-in-human study of microRNA-loaded minicells as a treatment for recurrent malignant pleural mesothelioma patients by van Zandwijk and colleagues (1). The rationale of this interesting study relies on the potential inhibition of tumor growth through the restoration of miR-16 with a miRNA mimic that is delivered into the tumor cells with TargomiRs (EGFR targeted minicells) (2,3). It has been demonstrated that several members of the miR-16 family are downregulated in malignant mesothelioma. These miRNAs act as tumor suppressors and their primary targets are genes involved in cancer progression including BCL2, CDK1 and JUN.

Briefly, 26 pleural mesothelioma patients received at least one Targomir dose, the maximum tolerated dose was 5×10^9 TargomiRs once weekly, the safety profile was acceptable and 1 of 22 patients had an objective response that lasted 32 weeks. Based on these results, the authors conclude that TargomiRs merit further clinical development and propose to test the combination with chemotherapy or immune checkpoint inhibitors.

The relevance of the study is remarkable: while incidence of malignant mesothelioma is increasing worldwide (4), it remains an untreatable form of lethal cancer in which palliative chemotherapy is the only available therapy for most patients (5,6). In this context, innovative treatment options are urgently needed and the first clinical use of miR-16 mimic represents a new therapeutic approach.

A critical review of the data presented in this paper raised two main questions:

(I) What is the precise mechanism of action of this treatment?

(II) How does this new therapeutic approach fit in the current mesothelioma treatment strategies landscape?

In the following paragraphs we will try to answer those questions in a succinct way.

Mechanism of action

The role of miRNAs in cancer has been well established in basic and preclinical models but its translation to the clinical setting remains challenging due to the difficulty in achieving a specific, safe and efficient way to deliver them into the tumor sites. Some of the main hurdles are: off-target effects, fast enzymatic nucleic acid degradation in peripheral blood and the fibrous nature of tumors (7,8), particularly pleural mesothelioma. To circumvent these problems authors have used a sophisticated vector, TargomiRs, in which the miR-16 mimic is loaded.

TargomiRs are nonliving bacterial minicells (nanoparticles) that serve as drug delivery vehicles (9). They function as leak resistant micro-reservoir carriers that allow efficient packaging of a range of different molecules, including nucleic acids. These characteristics allow the intravenous administration of the miR-16 mimic avoiding the enzymatic degradation in the peripheral blood. In order to skip undesirable off-target effects, these minicells can be directed to a given target with bispecific antibodies. In

this paper, EGFR targeting with panitumumab was selected based on the fact that mesothelioma cells frequently overexpress that receptor in the cell membrane.

However, in the discussion authors recognize that they were unable to confirm *in vivo* that the miR16-mimic was actually delivered to tumor sites or to demonstrate the predicted inhibition of BCL2, CDK1 and JUN in the tumor cells. Post treatment biopsies for comprehensive Western Blot assays will be key in the future development of this therapeutic approach.

At this point, an alternative possibility for the antitumor effect of this agent is hypothesized: an immune mediated response. On the one hand, it has been described that miRNAs are key regulators of immune cell development and function, as well as disease pathogenesis (10). Furthermore, mir-16 mimic is formed by double-stranded RNAs and these molecules elicit a strong innate immune response that could be responsible for activating viral defense genes, unchaining an anticancer immune response. On the other hand, the fact that many of the side effects observed in this trial consist of inflammatory reactions, it supports the idea of an immunologic effect. The bacterial origin of the drug delivery vehicle is highlighted by the authors as a potential cause of the inflammatory effects, arguing that the same side effects have been observed in other clinical trials testing the same vector, loaded not with RNA-based agents, but with cytotoxic drugs. In summary, there are many hints of potentially beneficial, but also toxic, immune effects related to the use of miR-16 mimic loaded TargomiRs.

Less relevant, but not negligible, is the potential antitumor efficacy mediated by the EGFR antibody used to specifically direct the minicells. Although there are no published data available with panitumumab in the treatment of mesothelioma, cetuximab has been evaluated in the preclinical setting and showed promising activity, mainly through the immunologic mechanism of antibody-dependent cellular cytotoxicity (11). Nimotuzumab, another EGFR directed antibody, has also been recently evaluated and showed positive results in animal models (12). However, the use of EGFR antibodies has had no further clinical development in pleural mesothelioma.

Current mesothelioma landscape

A thorough review of the currently active trials in pleural mesothelioma reveals that a great variety of therapeutic approaches are in early phases of development.

In order to classify them, we could use the following categories based on general mechanisms of action: immunotherapy (including immune checkpoint blocking antibodies, vaccines, cell therapy), gene therapy, oncolytic virotherapy, targeted therapy (including small molecule tyrosine-kinase inhibitors, antibodies and antibody-drug conjugates), physics-based therapy (including tumor-treating fields, cryotherapy, photodynamic therapy, hypertermia and pressurized intrapleural aerosols) and chemotherapy. A complete review of the most promising agents are out of the focus of this editorial but these recent reviews will be helpful for the interested reader (13,14).

van Zandwijk and colleagues miR-16 mimic loaded minicells are the only miRNA based therapy being developed in mesothelioma to our knowledge. Furthermore, if we consider the proposed immunologic effect of TargomiRs and their EGFR targeted specificity, they show a mixed mechanism of action fitting into three categories at the same time: gene therapy, immunotherapy and targeted therapy.

In the maelstrom of agents and strategies on development, immunotherapy seems the most appealing, with almost half of the clinical trials dedicated to it. Particularly, already published or reported clinical data on immune checkpoint inhibitors raise new hopes for patients and doctors. For example, pembrolizumab (an antiPD1 antibody) preliminary data reported an activity of 20% durable partial responses (PFS up to 12 months) (15) and nivolumab (another antiPD1 antibody) in combination with ipilimumab (antiCTLA-4 antibody) showed 26% of partial responses with a slight increase of severe toxicities when compared with nivolumab alone (16). Besides that, an Avelumab (anti PDL-1 antibody) clinical trial achieved 14.3% overall response rate in patients with PDL1 + tumors (17). Several trials with similar antibodies, including atezolizumab, durvalumab and tremelimumab, are being tested, and their results are eagerly-awaited. Based on these data, and in agreement with the authors, immune checkpoint inhibitors look like excellent partners to combine with miR-16 mimic TargomiRs.

Meanwhile, cisplatinum-pemetrexed chemotherapy is still the backbone of mesothelioma treatment and offers another excellent chance for combination in the search of wider and deeper clinical responses. The addition of bevacizumab to this combination showed improved efficacy but has not been fully embraced by mesothelioma-treating physicians, probably due to lack of financial coverage.

However, conducting clinical trials in pleural

mesothelioma is challenging due to the low (although increasing) prevalence of the disease, the variety of candidate therapies, the difficult radiological response assessment (18), and the quick clinical deterioration of mesothelioma patients after progression. Because of that, a careful next step is advisable in order to further develop miR-16 loaded TargomiRs. A smart, clean design with solid predictive biomarker assessment, effective toxicity management and detailed pharmaco-economic evaluation will be crucial for the successful implementation of this therapy in the clinical practice. In the discussion, authors propose to administer TargomiRs directly to the pleura in order to be able to safely increase the dose, but it is to be noted that intrapleural catheters will increase the complexity of the treatment and may not be available in many non-specialized centers.

In summary, van Zandwijk and colleagues successfully accomplished the first-in-human use of a miRNA-based therapy for pleural mesothelioma patients, showing that it is a safe strategy with promising activity that deserves to be tested in further clinical trials.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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