Commentary

Commentary on "MiRNA Expression Analysis of Pretreatment Biopsies Predicts the Pathological Response of Esophageal Squamous Cell Carcinomas to Neoadjuvant Chemoradiotherapy"

Mathieu Derouet, Gail E. Darling

[1]Latner Thoracic Laboratories, Toronto Medical Discovery Tower, Elizabeth St., Toronto Ontario, M5G 2C4, Canada; [2]Thoracic Surgery, University of Toronto, Toronto General Hospital, University Health Network, Toronto Ontario, M4G 2C4, Canada

Correspondence to: Gail E. Darling, MD, FRCSC, FACS, Professor Thoracic Surgery. University of Toronto, Toronto General Hospital, University Health Network, 200 Elizabeth St., 9N-955, Toronto Ontario, M4G 2C4, Canada. Email: gail.darling@uhn.ca.

Comment on: Wen J, Luo K, Liu H, *et al*. MiRNA Expression Analysis of Pretreatment Biopsies Predicts the Pathological Response of Esophageal Squamous Cell Carcinomas to Neoadjuvant Chemoradiotherapy. Ann Surg 2016;263:942-8.

Submitted Jun 16, 2016. Accepted for publication Sep 19, 2017.
doi: 10.21037/tcr.2017.02.48
View this article at: http://dx.doi.org/10.21037/tcr.2017.02.48

Esophageal cancer has now become the 8th most common cancer and the 6th most common cause of death in the world (1). In a recent publication on neoadjuvant therapy in esophageal adenocarcinoma patients (2) tumor stage after neoadjuvant therapy predicted survival after surgery, however some patients do not respond to neoadjuvant therapy and thus their definitive treatment is delayed without benefit. Unfortunately even those who have a complete pathologic response may still die of metastatic disease. Identification and validation of molecular/biological markers to predict response to therapy would be of major benefit to patients and their doctors.

Although clinical markers have been identified, none reliably distinguish patients who may benefit from neoadjuvant therapy from those who will not benefit. Molecular markers have not been well studied in esophageal cancer and in particular MicroRNAs (miRNA) are an under-studied molecular marker. The paper by Wen *et al*. (3) studied the miRNA expression in pretreatment biopsies to determine if a miRNA profile could be identified to predict pathological response. An important feature of this study was that only squamous cell cancers (ESCC) were included. It has been recognized that ESCC differs from adenocarcinoma of the esophagus (EAC) in many ways and that these two tumor types should not be grouped together in analyses.

The authors grouped all responders together (complete and partial responders) and compared these patients to those who were identified as non-responders based on >50% viable tumor cells in the resected specimen. There was no significant difference in disease specific survival between responders and non-responders. MiRNA analysis was performed on 27 pretreated biopsies. After microarray analysis and qPCR validation, they established a 10-miRNA signature that could differentiate responders from non-responders. This miRNA signature was then further evaluated through several complex statistical tests resulting in a 4 miRNA signature that could discriminate between non-responders and responders. The results were then validated using paraffin embedded samples from 79 previously resected cases.

This paper by Wen *et al*. reflects the recent interest of the potential of miRNA in esophageal cancer (4-6). A similar paper published by Skinner *et al*. demonstrated the potential of a 4-microRNA signature to predict response to therapy in esophageal adenocarcinoma patients (7). Despite the impressive results shown in the paper by Wen *et al*, there are several points which need to be addressed. First, as the authors mentioned, the analysis was based on a small number of pretreatment biopsies although the validation set was significantly larger. One of the difficulties in working in esophageal cancer research is the relatively small patient population compared to more common cancers such as breast or colon or lung cancer. A second problem has been the inclusion of both ESCC and EAC in most studies. Wen and colleagues have limited their study to ESCC only.

In evaluation of miRNA an endogenous control must be

used. There has been significant variability in selecting a miRNA for endogenous control in other studies. However, in this paper, the authors used 3 different miRNAs, all of which have been previously validated. Nonetheless, comparing studies is difficult when the endogenous controls are different. This issue could potentially be the reason for the discrepancies between miRNA profiling studies.

One challenge in using miRNA profiles is that the role of a specific miRNA may be variable and may be organ and/or disease specific. Thus in one tumor type a miRNA may act as a tumor suppressor but may act as an oncogene in a different tumor. This makes it difficult to extrapolate the role of various miRNAs from one study to the next (8).

The study by Wen and colleagues provides us with a potential molecular profile to guide treatment in ESCC. The miRNA profile identified will need to be further validated by other investigators before it can be used clinically. As with promising gene signatures, the 4 miRNA signature identified by Wen and colleagues is just a beginning.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Qing-Yuan Huang (Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.02.48). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
2. Davies AR, Gossage JA, Zylstra J, et al. Tumor stage after neoadjuvant chemotherapy determines survival after surgery for adenocarcinoma of the esophagus and esophagogastric junction. J Clin Oncol 2014;32:2983-90.
3. Wen J, Luo K, Liu H, et al. MiRNA Expression Analysis of Pretreatment Biopsies Predicts the Pathological Response of Esophageal Squamous Cell Carcinomas to Neoadjuvant Chemoradiotherapy. Ann Surg 2016;263:942-8.
4. Ko MA, Zehong G, Virtanen C, et al. MicroRNA expression profiling of esophageal cancer before and after induction chemoradiotherapy. Ann Thorac Surg 2012;94:1094-102; discussion 1102-3.
5. Tan C, Qian X, Guan Z, et al. Potential biomarkers for esophageal cancer. Springerplus 2016;5:467.
6. Harada K, Baba Y, Ishimoto T, et al. The role of microRNA in esophageal squamous cell carcinoma. J Gastroenterol 2016;51:520-30.
7. Skinner HD, Lee JH, Bhutani MS, et al. A validated miRNA profile predicts response to therapy in esophageal adenocarcinoma. Cancer 2014;120:3635-41.
8. Cortez MA, Bueso-Ramos C, Ferdin J, et al. MicroRNAs in body fluids--the mix of hormones and biomarkers. Nat Rev Clin Oncol 2011;8:467-77.

Cite this article as: Derouet M, Darling GE. Commentary on "MiRNA Expression Analysis of Pretreatment Biopsies Predicts the Pathological Response of Esophageal Squamous Cell Carcinomas to Neoadjuvant Chemoradiotherapy". Transl Cancer Res 2017;6(Suppl 1):S1-S2. doi: 10.21037/tcr.2017.02.48

