The Place of Biological Markers to Predict the Response after Neoadjuvant Treatment in Esophageal Cancer

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Abstract

Esophageal cancer remains one of the most severe malignancies in terms of overall survival despite the introduction of novel radiation regimens and chemotherapy agents. Many of the patients are diagnosed in advanced cases in which a multimodal treatment protocol is applied, finding the biomarkers that are involved in the resistance to neoadjuvant treatment could select the subgroup of patients that could be submitted either to surgical treatment or to an experimental drug trial. Hereby, we reviewed the potential biomarkers (immunohistochemical, blood-based, miRNA markers and gene expression profiling) that promised novel therapeutic pathways protocols.

Background

Esophageal cancer represents one of the most aggressive solid tumor, nowadays it represents the 5th most frequent cause of death in males and the 8th cause of death in female patients [1]. Despite the fact that there are recent developments regarding surgical, radio and chemotherapy for esophageal cancer overall survival rates remains around 40% [2]. Current guidelines based on large randomized studies recommends the usage of neoadjuvant treatment for advanced newly diagnosed esophageal tumors, the subset of patients who benefit the most in terms of overall survival are the patients which presented a complete response to neoadjuvant treatment protocol [3,4]. Based on published studies 60 to 70% of patients do not develop a significant response to neoadjuvant treatment (non-responders) with the price of severe side effects of radio and chemotherapy [5,6]. Based on those results, a subset of patients with resectable disease could benefit from a radical surgery protocol. For the moment there are no reliable clinical, biological and tumoral characteristics that could predict the tumor response to neoadjuvant treatment. Several tumor markers were studied in the last years in order to characterize their ability for neoadjuvant treatment response prediction. We, hereby present the most important markers in term of best yet prediction ability based on published studies.

Immunohistochemistry Markers

One of the best advantages of histological examination of surgical specimen in a solid tumor is the spatial characterization of tumor architecture with the precise identification of tumor fragments in which more precise staining will be performed. Solid tumors are characterized by the presence of a small number of stem tumor cells, tumor initiating cells or stem-like neoplastic cells [7,8]. The role of immunehistochemical biomarkers is important to elucidate the pathways for epidermal growth, neo angiogenesis and apoptosis. The most investigated markers in esophageal cancer were: epidermal growth factor receptor (EGFR), p53, vascular endothelial growth factor (VEGF) and estrogen receptor. A study published by Smit et al. [9] showed that the cell subpopulation CD44+/CD24- has a higher division rate and tend to be resistant to radiotherapy compared to CD44+/CD24+ cells and thus the clinical use of identification of this cell subtype.

There were some studies regarding the HER2/neu and EGFR expression in esophageal cancer and the response to radio/chemotherapy,

some authors demonstrated a correlation between HER2/neu and EGFR expression and resistance to treatment [10] and other study showed that there is no significant difference in response between patients with or without HER2/neu and EGFR expression [11].

Single Nucleotide Polymorphism

By analyzing human genome it became clear that genetic variations are more extended that the initial estimation [12]. The most common variation in human genome is the substitution of a single base, which is named single nucleotide polymorphism. A study from 2006 that included 210 patients with esophageal cancer showed that among genes involved in DNA repair, the R399Q variant on XRCC1 gene was significantly associated with the absence of treatment response and a poor overall survival [13]. Brabender et al. showed that RNA expression of ERCC1 in peripheral blood could be a predictor for response in esophageal cancer [14].

Micro-RNA

Micro-RNA (miRNA) represents a short sequence (between 19 and 24 nucleotides) of non-codant RNA involved in gene expression regulation through inhibition of RNAm translation [15] and can participate in physiological processes such as cell differentiation, proliferation, metabolism and apoptosis. Recent studies have showed that abnormal expression of miRNA detected in esophageal cancer has a strong predictive value [16,17]. A study published in 2013 [18] showed that the pre therapeutic expression of miRNA-192 and miRNA-194 was significantly correlated with histological response to neoadjuvant treatment for squamous cell esophageal carcinoma. By using small

specimens from tumor biopsies before treatment, Ko et al. showed that the profile of miRNA expression was different between complete responders and non-responders [19]. Tanaka et al. studied the level of miRNA-21, miRNA-145 and miRNA-200c in the serum of 64 patients with esophageal cancer in which multimodal treatment was applied [20]. The results were that a high expression of miRNA-200 is correlated with a poor response to treatment, results that were confirmed by a study conducted on 98 patients which showed that miRNA-200c is involved in chemotherapy resistance [21].

Gene Expression Profiling Biomarkers

Nowadays, gene expression microarray that generates a quantitative expression of genes can predict the response to neoadjuvant treatment in esophageal cancer [22]. Mahlet et al. investigated the gene expression profile in 13 patients, which were considered to be the most responsive and nonresponsive to standard chemo and radiotherapy protocol [23] and there were identified 5 genes (EPB41L3, RNPC1, RTKN, STAT5B and NMES1) as predictive biomarkers to neoadjuvant treatment for esophageal cancer with an overall accuracy of 95%. Another study by Luthra et al. in which were analyzed the genetic profiles in endoscopic biopsies specimens of 19 patients with esophageal cancer showed that the expression level of 3 genes (PERP, S100A2 and SPRR3) can predict the complete response with a sensibility of 86% and a specificity of 85% [24]. Motoori et al. identified a subset of 199 genes with an overall accuracy of 82% for treatment response based on samples from 25 patients with squamous cell carcinoma [25]. A more comprehensive study that included 46 patients (both adenocarcinomas in 25 patients and 21 squamous cell tumors) identified 32 genes that could be used for prediction for response to multimodal treatment for squamous cell tumors and a negative prediction model was created for adenocarcinomas [26]. Those studies showed that gene expression profile represents a strong tool for patient selection in order to give the best chance to cure treatment protocol.

Serum Biomarkers

Using the serum biomarkers represents a fast, relatively low cost and easy to reproduce method for patient selection. Makuuchi et al. studied the serum levels of more than 84 cytokines in 37 patients with squamous cell carcinoma and showed that the serum levels of receptors for Il-6 was significantly higher in patients with complete clinical response to neoadjuvant treatment, thus a strong correlation between the serum levels of Il-6 receptors and the response to treatment [27]. Those observations could suggest that systemic inflammation could be a possible mechanism of resistance to treatment. Brabender et al. evaluated the expression of thymidylate synthase and dihydropyrimidine dehydrogenase in peripheral blood of 29 patients of patients with esophageal cancer in which neoadjuvant treatment was applied and showed that an elevated expression of thymidylate synthase is associated with a minimal response to treatment and that the dihydropyrimidine dehydrogenase is not significantly associated with the treatment response [28]. One of the most useful advantages is that the specificity of response prediction is close to 100% when the levels of thymidylate synthase and dihydropyrimidine dehydrogenase are evaluated together.

Usual Blood Tests

Although they have a low sensibility and sensitivity, usual blood test are the most utilized methods to select the patients for a specific treatment protocol. Sato et al. analyzed the correlation between the neutrophil to lymphocytes ratio (NLR) before treatment and the response to neoadjuvant chemotherapy for esophageal cancer [29] and found out that a NLR<2.2 was significantly correlated with a pathologic response in 56% of cases and for NLR>2.2 in 21% of cases. Similar results were published by Noble [30] which showed that systemic inflammatory markers and nutritional status indicators can predict the response to neoadjuvant treatment.

Conclusion

Tailoring the best treatment protocol for a patient newly diagnosed with esophageal cancer can be sometimes difficult. Finding the subset of patients which can best benefit from the neoadjuvant treatment by using the actual clinical and biological criteria requires the addition of one or many more accurate biomarkers. The down size of the novel biomarkers is the high costs and availability; in present times those biomarkers are used only for research purposes. In order to offer the best treatment option it is necessary an interdisciplinary cooperation for all cancer patients.

Conflict of Interest

The authors report no conflict of interest. All the authors had a significant contribution to this paperwork.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. CA Cancer J Clin 61: 69-90.

2. Rice TW, Rusch VW, Apperson-Hansen C, Allen MS, Chen LQ, et al. (2009) Worldwide oesophageal cancer collaboration. Dis Oesophagus 22: 1-8.

3. Kaklamanos IG, Walker GR, Ferry K, Franceschi D, Livingstone AS (2003) Neoadjuvant treatment for resectable cancer of the oesophagus and the gastro oesophageal junction: a meta-analysis of randomized clinical trials. Ann Surg Oncol 10: 754-761.

4. Fiorica F, Di Bona D, Schepis F, Licata A, Shahied L, et al. (2004) Preoperative chemo radiotherapy for oesophageal cancer: A systematic review and meta-analysis. Gut 53: 925-930.

5. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, et al. (2007) Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol 8: 226-234.

6. Nguyen NP, Krafft SP, Vos P, Vinh-Hung V, Ceizyk M, et al. (2011) Feasibility of tomotherapy for Graves' ophthalmopathy: Dosimetry comparison with conventional radiotherapy. Strahlenther Onkol 187: 568-574.

7. O'Brien CA, Pollett A, Gallinger S, Dick JE (2007) A human colon cancer cell capable of initiating tumour growth in immune deficient mice. Nature 445:106-110.

8. Vermeulen L, De Sousa EMF, van der Heijden M, Cameron K, de Jong JH, et al. (2010) Wnt activity defines colon cancer stem cells and is regulated by the microenvironment. Nat Cell Biol 12: 468-476.

9. Smit JK, Faber H, Niemantsverdriet M, Baanstra M, Bussink J, et al. (2013) Prediction of response to radiotherapy in the treatment of oesophageal cancer using stem cell markers. Radiother Oncol 107: 434-441.

10. Akamatsu M, Matsumoto T, Oka K, Yamasaki S, Sonoue H, et al. (2003) c-erbB-2 oncoprotein expression related to chemoradioresistance in oesophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 57: 1323-1327.

11. Arsenijevic T, Micev M, Nikolic V, Gavrilovic D, Radulovic S, et al. (2012) Is there a correlation between molecular markers and response to neoadjuvant chemoradiotherapy in locally advanced squamous cell oesophageal cancer? J BUON 17: 706-711.

12. Risch NJ (2000) Searching for genetic determinants in the new millennium. Nature 405: 847-856.

13. Wu X, Gu J, Wu TT, Swisher SG, Liao Z, et al. (2006) Genetic variations in radiation and chemotherapy drug action pathways predict clinical outcomes in oesophageal cancer. J Clin Oncol 24: 3789-3798.

14. Brabender J, Vallbohmer D, Grimminger P, Hoffmann AC, Ling F, et al. (2008) ERCC1 RNA expression in peripheral blood predicts minor histopathological response to neoadjuvant radio-chemotherapy in patients with locally advanced cancer of the oesophagus. J Gastrointest Surg 12: 1815-1821.

15. Bhatti I, Lee A, Lund J, Larvin M (2009) Small RNA: A large contributor to carcinogenesis? J Gastrointestinal Surg 13: 1379-1388.

16. Hu Y, Correa AM, Hoque A, Guan B, Ye F, et al. (2011) Prognostic significance of differentially expressed miRNAs in esophageal cancer. Int J Cancer 128: 132-143.

17. Akagi I, Miyashita M, Ishibashi O, Mishima T, Kikuchi K, et al. (2011) Relationship between altered expression levels of MIR21, MIR143, MIR145, and MIR205 and clinicopathologic features of esophageal squamous cell carcinoma. Dis Esophagus 24: 523-530.

18. Odenthal M, Bollschweiler E, Grimminger PP, Schroder W, Brabender J, et al. (2013) MicroRNA profiling in locally advanced oesophageal cancer indicates a high potential of miR-192 in prediction of multimodality therapy response. Int J Cancer 133: 2454-2563.

19. Ko MA, Zehong G, Virtanen C, Guindi M, Waddell TK, et al. (2012) MicroRNA expression profiling of esophageal cancer before and after induction chemo radiotherapy. Ann Thorac Surg 94: 1094-1102.

20. Tanaka K, Miyata H, Yamasaki M, Sugimura K, Takahashi T, et al. (2013) Circulating miR-200c levels significantly predict response to chemotherapy and prognosis of patients undergoing neoadjuvant chemotherapy for oesophageal cancer. Ann Surg Oncol 20: S607-615.

21. Hamano R, Miyata H, Yamasaki M, Kurokawa Y, Hara J, et al. (2011) Overexpression of miR-200c induces chemo resistance in oesophageal cancers mediated through activation of the Akt signaling pathway. Clin Cancer Res 17: 3029-3038.

22. Quackenbush J (2006) Microarray analysis and tumour classification. N Engl J Med 354: 2463-2472.

23. Maher SG, Gillham CM, Duggan SP, Smyth PC, Miller N, et al. (2009) Gene expression analysis of diagnostic biopsies predicts pathological response to neoadjuvant chemo radiotherapy of oesophageal cancer. Ann Surg 250: 729-737.

24. Luthra R, Wu TT, Luthra MG, Izzo J, Lopez-Alvarez E, et al. (2006) Gene expression profiling of localized oesophageal carcinomas: association with pathologic response to preoperative chemo radiation. J Clin Oncol 24: 259-267.

25. Motoori M, Takemasa I, Yamasaki M, Komori T, Takeno A, et al. (2010) Prediction of the response to chemotherapy in advanced oesophageal cancer by gene expression profiling of biopsy samples. Int J Oncol 37: 1113-1120.

26. Duong C, Greenawalt DM, Kowalczyk A, Ciavarella ML, Raskutti G, et al. (2007) Pre-treatment gene expression profiles can be used to predict response to neoadjuvant chemo radiotherapy in oesophageal cancer. Ann Surg Oncol 14: 3602-3609.

27. Makuuchi Y, Honda K, Osaka Y, Kato K, Kojima T, et al. (2013) Soluble interleukin-6 receptor is a serum biomarker for the response of oesophageal carcinoma to neoadjuvant chemo radiotherapy. Cancer Sci 104: 1045-1051.

28. Brabender J, Metzger R, Vallbohmer D, Ling F, Neiss S, et al. (2012) Roles of thymidylate synthase and dihydropyrimidine dehydrogenase expression in blood as predictors of response to multimodal therapy in oesophageal cancer. Surgery 151: 306-312.

29. Sato H, Tsubosa Y, Kawano T (2012) Correlation between the pre therapeutic neutrophil to lymphocyte ratio and the pathologic response to neoadjuvant chemotherapy in patients with advanced oesophageal cancer. World J Surg 36: 617-622.

30. Noble F, Hopkins J, Curtis N, Kelly JJ, Bailey IS, et al. (2013) The role of systemic inflammatory and nutritional blood-borne markers in predicting response to neoadjuvant chemotherapy and survival in oesophagogastric cancer. Med Oncol 30: 596.