A germline predictive signature of response to platinum chemotherapy in esophageal cancer

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Platinum-based neoadjuvant therapy is the standard treatment for esophageal cancer (EC). At present, no reliable response markers exist, and patient therapeutic outcome is variable and very often unpredictable. The aim of this study was to understand the contribution of host constitutive DNA polymorphisms in discriminating between responder and nonresponder patients. DNA collected from 120 EC patients treated with platinum-based neoadjuvant chemotherapy was analyzed using drug metabolism enzymes and transporters (DMET) array platform that interrogates polymorphisms in 225 genes of drug metabolism and disposition. Four gene variants of DNA repair machinery, 2 in *ERCC1* (rs11615; rs3212986), and 2 in *XPD* (rs1799793; rs13181) were also studied. Association analysis was performed with pTest software and corrected by permutation test. Predictive models of response were created using the receiver-operating characteristics curve approach and adjusted by the bootstrap procedure. Sixteen single nucleotide polymorphisms (SNPs) of the DMET array resulted significantly associated with either good or poor response; no association was found for the 4 variants mapping in DNA repair genes. The predictive power of 5 DMET SNPs mapping in *ABCC2*, *ABCC3*, *CYP2A6*, *PPARG*, and *SLC7A8* genes was greater than that of clinical factors alone (area under the curve (AUC) = 0.74 vs 0.62). Interestingly, their combination with the clinical variables significantly increased the predictivity of the model (AUC = 0.78 vs 0.62, $P = 0.0016$). In conclusion, we identified a genetic signature of response to platinum-based neoadjuvant chemotherapy in EC patients. Our results also disclose the potential benefit of combining genetic and clinical variables for personalized EC management. (Translational Research 2016;171:29–37)

Abbreviations: EC = esophageal cancer; EADC = esophageal adenocarcinoma; ESCC = esophageal squamous cell carcinoma; DMET = drug metabolism enzymes and transporters; ROC = receiver operating characteristics; AUC = area under the curve; RECIST = response evaluation criteria in solid tumors; CR = complete response; PR = partial response; SD = stable

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disease; PD = progressive disease; SNP = single nucleotide polymorphism; TNM = tumor-node-metastasis; OR = odds ratio; 95% CI = 95% confidence interval; IQR = interquartile range; R = responders; NR = nonresponders; CTRT = chemoradiotherapy; CT = chemotherapy

AT A GLANCE COMMENTARY

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Background

Esophageal cancer (EC) is an aggressive disease associated with a poor prognosis. Platinum-based therapeutic treatment followed by surgery is the current regimen in almost all patients with a resectable tumor. Unfortunately, prognosis remains poor, and response cannot be foreseen by clinical factors only. Thus, additional markers predicting the outcome to neoadjuvant therapy are needed.

Translational Significance

In this work, we investigate the impact that host genetic variables might have on the response, by analyzing, with the pharmacogenetic DMET array, a cohort of 120 EC patients. We identified a 5-SNP signature discriminating between responder and nonresponder patients that increased the predictive ability of the clinical variables. These findings might have an important impact for an *a priori* identification of EC patients that would not benefit from platinum-based neoadjuvant therapy and that, therefore, should be addressed to a more appropriate therapeutic planning.

INTRODUCTION

Esophageal cancer (EC) is a highly lethal malignancy, usually diagnosed at an advanced stage.[1] Surgery was the standard of care for potentially resectable neoplasia, preceded by neoadjuvant chemotherapy when the reduction of the tumor mass was deemed necessary for optimal surgery.[2,3] Nowadays, the guidelines for EC management recommend platinum-based neoadjuvant treatment followed by surgery in almost all patients with a resectable tumor. Based on several trials, this change in therapeutic strategy seems to have improved survival rates at 5 years.[4-6] Nevertheless, the response to neoadjuvant chemotherapy remains unpredictable with a significant interindividual variability, ranging from a complete pathologic response (defined as no residual cancer cells in the resected specimen), to a forthright progression. Clinical parameters, such as TNM classification, tumor location, and tumor grade or stage, do not effectively foresee the response to neoadjuvant chemotherapy.[7] The identification of biomarkers predictive of neoadjuvant treatment outcome would be beneficial to EC management, in particular for those patients who do not respond, as they might lose precious time to benefit from other possible treatments and might suffer in vain from side effects. Response to chemotherapy is a function of several factors including tumor and host genetic characteristics. Tumor genetics is certainly important for targeted therapy, but when only a nontargeted approach is feasible, the genetic background of the host might play a major role. In addition, the germline variants are good candidates for predicting therapeutic response because of their stability over time and the simplicity of sampling.

Several studies have associated genetic polymorphisms with the efficacy of platinum treatment in different tumor types including EC. Most used a candidate gene approach that required an *a priori* knowledge and selection of the genetic variants. These studies mainly focused on DNA repair genes assuming that a suboptimal DNA repair capacity may have an impact on therapeutic response and/or on overall survival.[8-10] Among these genes, particular attention has been devoted to *ERCC1* and *XPD* variants that have been reported to play a part in gamma radiation damage repair.[11,12] In addition, the glutathione S-transferase family gene variants were largely studied as possible predictive markers of platinum-based therapy,[10,13-16] as well as *TP53* and its regulator *MDM2* involved in cell cycle regulation and death.[17,18] To date, only limited data exist on the influence of pharmacokinetic and pharmacodynamic genes in platinum-based therapies.[10,19-21] Platinum pharmacokinetics is characterized by limited metabolism and extensive renal elimination or biliary excretion, with up to 4-fold differences in drug clearance among patients.[22] Furthermore, its antitumor efficacy has been directly linked to accumulation in tumor cells, and previous data have suggested that uptake of the drug across the cellular membrane is partially mediated by specific carrier proteins.[23-25]

Here, we report the results of a marker discovery study carried out using the pharmacogenetic Drug Metabolism Enzymes and Transporters (DMET) array in a cohort of EC patients treated with platinum-based