CHAPTER 11

PREDICTION OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN CARCINOMAS OF THE UPPER GASTROINTESTINAL TRACT

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Abstract: Multimodal treatment protocols are increasingly employed to improve the survival of patients with locally advanced adenocarcinomas of the upper gastrointestinal tract, however, only 30–40% per year of the patients respond to 5-FU and cisplatin-based neoadjuvant chemotherapy. The goal of our studies is the identification of reliable genetic markers, on the genomic DNA-level, mRNA, or protein level that could predict response of upper gastrointestinal carcinomas prior to neoadjuvant chemotherapy.

In esophageal carcinomas, a higher gene expression of methylenetetrahydrofolate reductase (MTHFR), an enzyme involved in folate metabolism, was more frequently found in responding patients. In addition high gene expression of caldesmon and of the two drug carrier proteins, MRP1 and MDR1 was associated with response to therapy. By performing a genome-wide profiling on the protein level in a small group of patients, new potential markers were identified, which have to be validated in ongoing studies.

In gastric carcinomas, mutations of the p53 gene revealed no association with response or survival, but tumors with a high rate of loss of heterozygosity (LOH), determined by microsatellite analysis, showed a better response to a cisplatin-based chemotherapy. Analysis of expression of 5-FU-(e.g., TS, DPD, and TP) and cisplatin-(e.g., ERCC1, ERCC4, GADD45A, and KU80) related genes, demonstrated an association of DPD expression with response and survival. The combined consideration of TP and GADD45 gene expression, showed the most obvious association with therapy response in this tumor.

Our studies point to promising markers with potential use for chemotherapy response prediction of adenocarcinomas of the upper gastrointestinal tract, but prospective studies for validation are necessary.

Key words: Neoadjuvant chemotherapy, carcinomas, gastrointestinal tract, LOH

1. INTRODUCTION AND OBJECTIVE

Multimodal treatment protocols are increasingly employed to improve the survival of patients with locally advanced adenocarcinomas of the esophagus and stomach. Neoadjuvant chemotherapeutic treatment, mainly based on cisplatin and 5-FU, has been used since 1989 in several clinical trials and recently, a statistically significant improvement in respect to resectability, progression-free and overall survival in operable gastric and lower esophageal cancer has been demonstrated in a large randomized, controlled phase III trial (MAGIC trial) [1]. However, only 30–40% of the patients respond to therapy and the majority of patients undergo several month of toxic, expensive therapy without survival benefit. In particular, in the case of esophageal carcinomas, it has been shown that patients with nonresponding tumors seem to have an even worse prognosis than patients treated by surgery alone, which may be related to therapy-induced side effects, selection of chemotherapy-resistant, more aggressive tumor cells and delay of surgery [2]. Thus, the identification of reliable genetic markers that could predict response is highly demanding.

Several molecular markers had been investigated as potential response predictors. Thymidylate synthase as the target enzyme for 5-FU has been widely studied for 5-FU-containing regimens in gastrointestinal cancer, but the results are inconsistent [3,4,5]. Dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP) are two other important regulatory enzymes involved in the degradation of 5-FU, and low levels of DPD have been shown to be associated with response in gastric carcinoma [5,6], whereas conflicting results have been reported for TP.

The other major component used for the treatment of carcinomas of the upper gastrointestinal tract is cisplatin, which supposedly directly damages DNA. A significant association of the gene expression of the nucleotide excision enzyme \textit{ERCC1}, which is involved in DNA repair, with response to neoadjuvant chemotherapy has been reported [4].

Other markers such as glutathione S-transferase, vascular endothelial growth factor and apoptosis-related genes have been such as \textit{bcl-2}, \textit{bax}, and \textit{p53} have mostly been studied by immunohistochemistry, and the results have been inconclusive, so that no markers has been found to be clinically relevant at present [3,7].

Thus, the goal of our studies is to identify effective molecular markers for response prediction for patients with esophageal and gastric carcinomas treated by a neoadjuvant chemotherapy. We are using different strategies based on one side, on targeted approaches to characterize pretherapeutic biopsies for tumor-specific molecular alterations on the genomic DNA and mRNA-level. We also analyze constitutional genetic factors, e.g., DNA-polymorphisms in therapy-related genes. On the other side, we perform a genome-wide profiling on the protein level, to identify new marker proteins.