New tricks for old biomarkers: thymidylate synthase expression as a predictor of pemetrexed activity in malignant mesothelioma

Combination of platinum compounds/pemetrexed has become the standard first-line treatment of malignant pleural mesothelioma (MPM) [1], but predictors of responsiveness to pemetrexed and/or cisplatin/carboplatin are still lacking. Recently, Righi et al. [2] retrospectively investigated the correlation between expression of thymidylate synthase (TS) and excision repair cross-complementation group-1 (ERCC1) in MPM patients treated with platinum compounds/pemetrexed. TS messenger RNA (mRNA) and protein levels inversely correlated with pemetrexed sensitivity in non-small-cell lung cancer (NSCLC) cells, as well as with outcome in NSCLC patients treated with pemetrexed-based chemotherapy. Low ERCC1 protein levels were associated with improved outcomes for adjuvant platinum-based chemotherapies in NSCLC.

However, no relationship was found between survival and ERCC1 protein levels, whereas patients with protein expression in the higher tertile and mRNA expression above median had significantly longer overall survival (OS) [2]. These data might be explained by the prognostic role of ERCC1, since a high ERCC1 protein increases the removal of DNA lesions, and therefore is correlated with longer disease-free survival and OS in surgical NSCLC patients.

We recently reported a correlation between TS-protein expression and both progression-free survival (PFS) and OS in 71 MPM patients treated with carboplatin + pemetrexed [3]. TS-expression correlated with shorter PFS [hazard ratio (HR) = 1.23; P = 0.004] and OS (HR = 1.21; P = 0.02). Although response assessment with conventional criteria is challenging in MPM, the disease control evaluation provides additional information as end point of drug activity. Indeed, TS was associated with a minor probability of disease control (odds ratio = 1.57; P = 0.012), and with PFS (HR = 1.24; P = 0.005) also in our model corrected for disease control.

Righi et al. [2] reported a correlation between TS-mRNA and protein expression, but no correlation between TS-mRNA and outcome. These results were ascribed to the small number of tumor cells in MPM specimens. Optimization/standardization of methodologies is crucial to identify and validate pharmacogenetic biomarkers. However, a consensus has not been reached as to the scoring of ERCC1 and TS immunostainings, and detailed procedures for experiment reproduction and correct interpretation of results are warranted.

Modern quantitative RT-PCR techniques amplify <100 bp-amplicons, allowing the use of mRNA extracted from archived paraffin-embedded tissues and biopsies, but should always be carried out with appropriate controls for intra/inter-laboratory validation. Indeed, standardization of both immunohistochemistry and PCR is necessary before larger retrospective/prospective studies can address the same pharmacogenetic question.

Last but definitely not least, expression and/or mutational status of other determinants of pemetrexed activity including dihydrop folate reductase, glycaminide ribonucleotide formyltransferase, influx transporters-reduced folate carrier, proton-coupled folate transporter, folylpoly-γ-glutamate synthetase, and the main functional TS and ERCC1 polymorphisms TSER-2R/3R and ERCC1-C118T should be evaluated [4, 5]. Contradictory conclusions about the impact of these polymorphisms on clinical outcome were reported. However, DNA is more amenable for collection/storage than a tissue sample, and genotyping results can easily be used to stratify patients. Therefore, assessing germline polymorphisms as markers of drug activity is still very appealing.

In conclusion, retrospective studies on candidate-predictive biomarkers in MPM specimens can provide strong rationale for future trials, and we await the final results of studies in carboplatin/pemetrexed-treated patients [3]. However, optimization/standardization of methodologies, as well as the use of larger and uniformly treated cohorts, and the incorporation of both emerging candidate biomarkers and genotype studies, are critical before prospective trials can identify the best biomarkers for personalized chemotherapy of MPM.

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