Precision medicine in the adjuvant treatment of gastric cancer

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Adjuvant chemotherapy is considered the standard of care after surgical resection in patients with stage IB–III gastric cancer in most Asian countries. The benefit of adjuvant chemotherapy after surgery over surgery alone in terms of overall and disease-free survival was confirmed in an individual-patient data meta-analysis[1] of 3838 patients treated in 17 randomised controlled trials. After surgery with curative intent, patients with gastric cancer receive postoperative chemotherapy to eradicate undetectable micrometastatic disease. Although this approach is effective in many neoplastic diseases, some patients might be overtreated because surgery is successful or because their tumours are not sensitive to a given type of chemotherapy. For example, in the CLASSIC trial,[2] although a significant benefit in overall survival was seen in patients treated with adjuvant chemotherapy (capecitabine plus oxaliplatin) versus patients treated with surgery alone, more than 50% of all randomised patients did not relapse at 5 years and around 70% were still alive at that time. These data suggest that some patients might be unnecessarily overtreated with adjuvant chemotherapy.

In *The Lancet Oncology*, Jae-Ho Cheong and colleagues[3] describe a predictive test for prognosis and response to adjuvant chemotherapy in patients with localised, resectable gastric cancer. The test is based on a four-gene real-time RT-PCR assay, which measures gene-expression levels in formalin-fixed, paraffin-embedded tumour tissues, and consists of two rule-based, single patient classifier algorithms for prognosis and prediction. To identify candidate genes, the authors used knowledge about the molecular classifications for gastric and colon cancers[4,5] and analysed gastric cancer transcriptome datasets. The aim of the test was to differentiate between three different prognostic groups (low, intermediate, and high risk) and two different chemotherapy-response groups (benefit and no benefit). In a two-step approach, the immune subtype (expression of *GZMB* and *WARS*) was first characterised, followed by the stem-like subtype (expression of *SFRP4*) that allows patient stratification according to risk or the epithelial subtype (expression of *CDX1*) that allows patient stratification according to chemotherapy response. This patient classification approach was evaluated in an internal cohort, and independently validated in a subset of patients from the CLASSIC trial.

The authors suggest that patients classified as immune high (positive expression of both *GZMB* and *WARS*) might not need adjuvant chemotherapy after surgery because their prognosis is favourable. In the validation cohort, patients predicted to benefit from adjuvant chemotherapy (chemotherapy benefit group, defined as immune low [negative for one or both of *GZMB* and *WARS*] and epithelial high [positive for *CDX1*]) had an improved overall survival at 5 years with the addition of adjuvant chemotherapy compared with those who received surgery alone. By contrast, in patients classified as the no-benefit group (who were immune low and negative for *CDX1*), the addition of chemotherapy did not improve overall survival compared with surgery alone. The authors recommend use of these single-patient classifiers to stratify patients with gastric cancer after surgery and predict the potential suitability for adjuvant chemotherapy.

We agree with Cheong and colleagues that this approach requires further investigation to be validated as a useful tool for precision medicine in the clinic. Future studies will need to assess the applicability and clinical value of the test. In particular, should this test be prospectively used in new randomised trials? Should patients be stratified to receive standard versus experimental treatments according to the results of a single prediction test for chemotherapy benefit? Do we have sufficient and robust information to use this test in all newly diagnosed patients to decide whether they need adjuvant chemotherapy? Are these data applicable to non-Asian patients with gastric cancer, in whom perioperative chemotherapy is preferred to postoperative treatment according to European Society for Medical Oncology (ESMO)[6] and other European guidelines? Could this genetic test be done at diagnosis in endoscopic samples?

Gastric cancer is a very heterogeneous disease. Genomic alterations detected in primary tumours could differ significantly from those observed in metastatic tumours or cell-free DNA.[7] This heterogeneity is one of the main barriers to the development and implementation of precision medicine strategies in gastric cancer, which is also hindered by insufficient

knowledge of the molecular characteristics of minimal residual disease.

In conclusion, this important research by Cheong and colleagues paves the way for implementation of precision medicine in other clinically relevant settings. Predictive tools could optimise adjuvant chemotherapy delivery in patients with resectable gastric cancer and avoid overtreatment. International collaborative effort is needed to speed up the implementation of precision medicine for patients with localised gastric cancer in clinical practice.

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