EBioMedicine 2 (2015) 780–781

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Is it Possible to Predict Benefit from 5FU Adjuvant Therapy in Stage III Colon Cancer Patients?

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For more than three decades patients diagnosed with stage III colorectal cancers have undergone adjuvant chemotherapy based on fluoropyrimidines (5-FU) and more recently in combination with oxaliplatin (Dienstmann et al., 2015). Overall that treatment has reduced the risk of tumor recurrence and improved survival for patients with resected colon cancer, but at present no validated biomarkers are available to predict the benefit of adjuvant chemotherapy in that group of patients. Up to now most efforts in CRC have been made to predict response to anti-EGFR therapy which is recommended now only to wild type KRAS and NRAS patients, but will most likely be followed by BRAF and PIK3CA in the near future (De Stefano and Carlomagno, 2014). For conventional 5-FU chemotherapy no companion biomarkers are available to predict therapy response, either for adjuvant or for curative protocols. Molecular heterogeneity of colon cancers is the main factor affecting the differential response to adjuvant chemotherapy. There are a lot of scientific articles reporting on biomolecules which can predict the response of that therapeutic approach. Among them MSI status (microsatellite instability) has already been shown to influence survival and response to adjuvant infusional 5-FU in colon cancer patients (Sargent et al., 2010) since patients with MSI tumors have better outcomes as compared with patients with microsatellite stable (MSS) tumors. However, the improved prognosis is abrogated in the face of adjuvant 5-FU treatment (Sargent et al., 2010). In addition, thymidylate synthetase, EGFR polymorphisms and many others have been shown to influence progression free survival and therefore response to adjuvant treatment to 5-FU, but frequently with controversial results. In spite of the extensive scientific production no consensus on the use of a particular biomarker for therapy benefit prediction has been obtained. One of the reasons is that in several studies the impact of adjuvant 5-FU chemotherapy referred to specific biomarkers was not addressed to specific subgroups (stage II versus stage III patients). The discrimination between stages II and III is relevant because these two stages differ both at the clinical–biological level and at the molecular level. Moreover, prognostic markers for stage III have been reported to have no significance for stage II cancers (Javle, 2010).

In this issue of *EBioMedicine*, Kandioler et al. analyzed TP53 mutations which produce a partial functionality of the protein (decreasing its transcriptional activity to less than 75%) in stage III colon cancer patients (Kandioler et al., in press). Relevant of this study is that the authors confined their analyses only to stage III patient and that they sub-classify that stage with respect to the number of the involved lymph nodes. They found a significant survival benefit of 5FU adjuvant chemotherapy only in N1 wild type patients in comparison to TP53 mutated ones. That benefit was lost when considering N2 patients highlighting that subgrouping is also relevant for N classes. There is the possibility as in breast cancers that N1 tumors behave as N0 ones. With respect to TP53 it plays at least 2 separate roles in the responses to therapeutic agents: it is an important component of cellular checkpoints, and it can mediate apoptosis. The response to individual drugs is determined by which of these 2 functions is paramount and for 5-FU the apoptotic effect is predominant (Bunz et al., 1999). The effect of mutation reducing TP53 activity seems to cause resistance to the apoptotic effects of FU, hence a diminished therapy benefit (Bunz et al., 1999). Nonetheless, the mutational status at TP53 could predict the benefit to adjuvant chemotherapy only in stage III patients with less than 3 positive lymph nodes and not in patients with more than 3 lymph nodes involved, for whom the authors did not expect any benefit from adjuvant chemotherapy. Surely, the response to all drugs, including 5-FU, is complex and unlikely to be completely explained by any single genetic alteration. Sub-classification in lymph node classes has proved to be a meaningful variable to understand response to 5-FU adjuvant chemotherapy. Possibly, tumors' heterogeneity with further additional "spatial" alterations in different metastatic sites could account for this result. The present study (Kandioler et al., in press) highlights that "early" advanced stage III tumors are different from N2 tumors and that N1 patients with TP53 mutations are less likely to respond to 5-FU adjuvant therapy in comparison to wild type. If confirmed it could have a considerable impact on clinical practice. Although those results are relevant additional studies are needed to sub-classify stage III colon cancer patients and define the group of patients who will benefit from adjuvant treatment in routine clinical practice.

Disclosure

The author declared no conflicts of interest.

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