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TAS-102 and the quest for predictive biomarkers

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Worldwide, colorectal cancer (CRC) is one of the leading causes of cancer-related deaths. Once metastases have developed (which happens eventually for the majority of patients), systemic chemotherapy becomes the mainstay of treatment, but options are limited: after progression on fluoropyrimidines, oxaliplatin, irinotecan, vascular endothelial growth factor and/or epidermal growth factor receptor inhibitors in case of RAS (Rat sarcoma virus) wildtype tumours, treatment with the multikinase inhibitor regorafenib could be considered. However, although regorafenib demonstrated statistically significant survival benefit in a randomised, placebo-controlled trial, the overall survival benefit was limited (1.4 months) and toxicity considerable,[1] stressing the unmet need for new therapeutic options for patients with treatment-refractory CRC.

TAS-102, a novel oral formulation of trifluorothymidine (trifluridine or TFT) and a thymidine phosphorylase inhibitor (TPI) to improve the bioavailability of TFT may provide such an option. Its primary cytotoxic mechanism is thought to be DNA incorporation, which could explain the antitumour effects in fluoropyrimidine-refractory tumours: after uptake in tumour cells, TFT is phosphorylated by thymidine kinase and converted into a DNA substrate. Incorporation of this substrate causes DNA dysfunction and strand break formation. Fluoropyrimidines can become DNA-incorporated as well, but their DNA-damaging ability is reduced by rapid cleave-off. Vice versa, TFT and fluoropyrimidines can both inhibit thymidylate synthase (TS), a central enzyme in DNA synthesis.[2]

The antitumour activity of TAS-102 in patients with treatment-refractory CRC was confirmed in the randomised, placebo-controlled phase III RECOURSE trial (Results of a multicenter, randomised, double-blind, phase III study of TAS-102 vs. placebo, with best supportive care (BSC), in patients with metastatic colorectal cancer (mCRC) refractory to standard therapies),[3] in which a small but significant survival benefit was observed for TAS-102-treated patients. Median progression-free survival (PFS) was 2.0 months (95% CI 1.9 to 2.1). Response duration, however, ranged from 0.1 to 78.0 weeks (ie, approximately 18 months), suggesting that a subgroup of patients exists in whom long-term disease control can be achieved. Given the limited average survival benefit, and the fact that the average is of little use for individual patients, identifying characteristics that distinguish patients who will benefit from TAS-102 from patients who will not is of uttermost importance.

Several potential predictors were evaluated within RECOURSE. According to the predefined subgroup analyses, survival benefit with TAS-102 was observed regardless of sex, age, geographical region, Eastern Cooperative Oncology Group performance status, primary tumour site, *KRAS*-mutation status, fluoropyrimidine resistance, time since diagnosis of first metastases, number of metastatic sites and number of prior regimens. Although reassuring that the observed benefit was maintained in all before-mentioned subgroups, these analyses do not provide the much needed insight that can help to improve TAS-102 patient selection.

Other biomarkers, not yet assessed by the RECOURSE trial, may thus be worth evaluating. Biomarkers that are known to affect fluoropyrimidine response may provide a logical first step, since TAS-102 and fluoropyrimidines both exert their antitumour effects by interfering with DNA synthesis.[2] This cytotoxic mechanism may explain why mismatch repair (MMR)-deficient tumours appear resistant to fluoropyrimidine-based treatment in the adjuvant setting: MMR enzymes play an important role in detecting fluoropyrimidine-induced DNA damage. MMR deficiency and the subsequent development of microsatellite instability (MSI) could thus be important determinants of fluoropyrimidine efficacy.[4] In stage II and III CRC, MSI does indeed correlate with non-response to

fluoropyrimidines.[5] The relation between MSI status and response to palliative chemotherapy in the metastatic setting, however, is less clear.[6] Given the before-mentioned similarities *and* differences between TAS-102 and fluoropyrimidines, we do believe the relation between MSI status and response to TAS-102 could be interesting to explore. Alternative DNA-based biomarkers that may deserve further attention include *BRAF* (v-Raf murine sarcoma viral oncogene homolog B) and homologous recombination (HR)-related genes. *BR*AF mutation status has been suggested as a negative-prognostic marker for CRC[7] and should therefore ideally be accounted for in efficacy analyses. Although RECOURSE did stratify patients according to KRAS status, BRAF status was unknown in 85% of patients and thus not accounted for. In addition, the prognostic value of these mutations appears to be different in MSI tumours,[8] again stressing the need to distinguish between microsatellite stable and instable tumours. HR-related genes seem to be logical candidate biomarkers along the same line of thinking. According to a recent study, genetic variants in the HR pathway are indeed associated with clinical outcome in TAS-102-treated patients with CRC.[9]

Laboratory values such as neutrophil count may further help to select patients most likely to benefit from TAS-102. Associations between therapy-induced neutropenia and antitumour efficacy have been described for other cytotoxic drugs and indications[10] and have been observed in TAS-102 treated patients with CRC as well.[11] In addition, carcinoembryonic antigen is known to have prognostic[12] and predictive value for CRC[13] and could thus provide another stratification factor. Finally, because clinical development preceding the RECOURSE trial focused mainly on Asian patients, stratification according to geographic–genetic background could also be of interest. Although RECOURSE did stratify patients by geographic subregion, these regions were dichotomised in 'Eastern' (Japan) and 'Western' (USA, Europe and Australia). Whether TAS-102 efficacy differs between patients from African, Hispanic or Hindustanic descent, for example, is thus unknown.

In conclusion and on a positive note, TAS-102 may be of additional value for patients with treatment-refractory CRC. However, biomarkers are needed to improve the therapeutic yield of this drug. Further research including the proposed candidate biomarkers may help to achieve this goal.

Contributors Both authors equally contributed to the design, literature search and writing.

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