Commentary

How to select colorectal cancer patients for personalized therapy

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The backbone of medical oncological therapy in patients with metastatic colorectal cancer (mCRC) is chemotherapy. In recent years, treatment of patients with mCRC has changed from "one strategy fits all" to a more personalized approach based on clinical characteristics and molecular profiling [1]. In the daily clinical practice, molecular profiling is used to identify therapeutically tractable alteration and to predict efficacy of targeted therapies. Presently, the molecular changes with immediate implication on the choice of therapy are RAS (KRAS and NRAS), BRAF and MSI status. Furthermore, new therapies directed against rare molecular alterations including HER-2 directed therapies and TRK-fusions are emerging and thus the importance of molecular profiling will grow.

In the meta-analysis accompanying this commentary, Bhullar and colleagues present data on biomarker concordance between primary and paired metastasis from 3565 patients (61 trials) with mCRC [2]. The liver was the most commonly biopsied metastatic site (n = 2276), followed by lymph nodes (n = 1123), and lung (n = 438) whereas biopsies from peritoneum were rather seldom (n = 132). They found an excellent agreement of 94% or higher for RAS and BRAF status and concluded correctly that molecular testing of either the primary or liver and lung metastasis is adequate. Discrepancies may partly depend on timing of metastases. Bhullar et al. could not account for the time between the primary tumor and metastasis but probably most of paired analyses were done in patient with synchronous mCRC as reported by others [2].

The most important marker in daily practice is the RAS status (around 45% of mCRC are RAS wildtype) as any mutation predict for no benefit of anti-EGFR therapy. The standard therapy in fit patients with left-sided RAS wildtype mCRC is a doublet or perhaps a triplet regimen with anti-EGFR therapy [3] but the optimal targeted therapy in patients with right sided tumors is still not established and in patients with RAS mutations, effective therapy and predictive markers are lacking [1].

The prognosis of mCRC patients depends on the localization of metastases as particularly peritoneal metastases is related to a worse prognosis as compared to other locations. In the present meta-analysis only 4% of patients included had peritoneal carcinomatosis. Therefore, to fully understand the genomics of the entire metastatic pattern of mCRC, future research should include analysis of all metastatic lesions.

BRAF^{V600E} mutation is found in approximately 10% of patients but may be found in as many as 20% in unselected patients [6]. Patients with a BRAF^{V600E} mutated tumor have a poor prognosis and derive limited benefit from standard therapy after first line therapy with a median PFS of only 2 months [7]. Unfortunately, there is no benefit of single agent BRAF-inhibition in mCRC patients because BRAF inhibition causes rapid feedback activation of EGFR leading to continued proliferation. This feedback stimulation may be overcome by simultaneous targeting multiple targets in the pathway, e.g. EGFR and MEK. A triple combination is evaluated in the 3-armed randomized BEACON trial and results are eagerly awaited.

The mismatch repair (MMR) system detects and repairs the mismatches that occur during DNA replication. Deficient MMR (dMMR) is found in approximately 15% of early stage CRC but in only 4–5% in patients with mCRC. Until recently, MMR status was primarily a helpful biomarker in patients with early stage CRC as patients with dMMR have better outcomes and derive no benefit of adjuvant 5-FU treatment. In contrast, patients with mCRC dMMR tumors have a poorer prognosis. However, these patients gain exceptional benefit from immunotherapy and consequently FDA approved check-point inhibitors in this small subgroup [4,5].

During the treatment lines, acquired resistance may develop - either because of treatment selection pressure or because of development of new mutations and/or other genomic changes. To increase knowledge on secondary resistance mechanisms and on the temporal heterogeneity we recommend more studies with biopsy of metastasis at the time of progressive disease. Another option to circumvent these problems is to search for genomic alterations in the circulation (liquid biopsy). Several head to head studies have demonstrated high concordance between blood-based testing versus standard tissue-based RAS testing methods [8]. Patients treated with anti-EGFR therapy almost inevitably develop resistance. The major mechanisms involve appearance of activating mutations in EGFR downstream effectors (KRAS, NRAS, or BRAF) and this may be reflected in ctDNA and thus acquired resistance to anti-EGFR therapy may be tracked by continuous analysis of ctDNA. Recently it was shown that mutant RAS clones arising during anti-EGFR therapy may disappear upon withdrawal of treatment pressure and therefore after a treatment break the tumor may become sensitive for rechallenge [9].

When implementing biomarkers in the routine clinical decisions it is of major importance to have solid and consistent evidence on as well technical, biological and clinical aspects. Therefore, the present study

[2] is of importance by demonstrating the concordance in molecular alterations between primary and metastasis in well-established markers and thereby confirming the current recommendations as stated in NCCN guidelines (version 4.2018) that biopsies from as well metastasis and primaries can be used for RAS and BRAF testing.

Disclosures

The authors declare no conflicts of interest.

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