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Allied therapies against *BRAF*-mutated advanced colon cancer: the right plans to win the battle

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In the era of molecular therapies, various targets in different pathways were identified and specific agents were developed with acceptable efficacy rates. *BRAF*, one of these targets from the family of MAPK, is mutated in different malignancies: melanomas, thyroid cancers, hairy cell leukemia, lung cancer and colorectal cancer [1]. Targeting this mutation with anti-*BRAF* agents showed interesting response rates in *BRAF*-mutated melanomas, thyroid cancers and hairy cell leukemia; however their outcomes were disappointing in this subgroup of colorectal cancers [2]. Thus, vemurafenib (anti-*BRAF*) was first approved as single-agent therapy in *BRAF*-mutated unresectable and metastatic melanoma; then, the combination of vemurafenib and trametinib (anti-MEK) showed better results than single agent in the same indication and was approved by the US FDA as a standard of care [3,4].

BRAF mutations occur in approximately 10% of colorectal cancers and are associated with a poor prognosis [5]. Different studies

demonstrated that *BRAF* and *KRAS* mutations were mutually exclusive. Patients with *BRAF*-mutated tumors had a significantly shorter median progression-free and median overall survival than patients with wild-type *BRAF* tumors, independently of received chemotherapeutic or targeted therapy regimen [2].

After identifying this group of colorectal cancer with poor prognosis, many efforts were done to explain the molecular and pathological characteristics of these tumors and the therapeutic impact on the choice of drugs that could seem beneficial for this subgroup of patients. Intensifying the treatment in these patients was one of the possibilities to counteract the aggressiveness and poor prognosis of this disease. TRIBE trial, which used intensive combined therapies, demonstrated that the FOLFOXIRI plus bevacizumab, as compared with FOLFIRI plus bevacizumab, improved the outcome in patients with metastatic colorectal cancer. The incidence of grade 3 or 4 neutropenia, diarrhea, stomatitis and peripheral

Colorectal Cancer

KEYWORDS

- anti-*BRAF* • bevacizumab
- FOLFIRINOX • prognosis
- treatment

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“...anti-PD-1 may also be promising agent by extrapolation of the results in melanoma...”

neuropathy was significantly higher in the experimental arm with FOLFOXIRI–bevacizumab compared with FOLFIRI–bevacizumab [6]. A recent update of this trial, with molecular subgroup analyses, concluded that this intensive regimen presents better results in all molecular subgroups including *BRAF*-mutated patients. In fact, this new combination showed higher progression-free survival and overall survival in *BRAF*-mutated colorectal cancers comparing with FOLFIRI–bevacizumab in this subgroup analysis based on TRIBE trial [7]. Based on these results, FOLFOXIRI–bevacizumab became the rationale standard of care of *BRAF*-mutated metastatic colorectal cancers, confirming the hypothesis that allied therapies seemed to present better outcomes than conventional treatments.

Many ongoing trials are evaluating the possibility of targeting *BRAF* mutation in this malignancy in combination with other targeted therapies, since there was no significant activity when anti-*BRAF* agents were used as single agent [8]. A combination of anti-*BRAF* and anti-MEK showed a better activity than single agents, without reaching the acceptable level of responses [9]. Updated results of Phase II trial presented in ASCO 2015 on a combination of anti-*BRAF*, anti-EGFR ± anti-MEK showed response rates of 26% in tri-therapies versus 10% in bi-therapies. The most frequently presented side effect of tri-therapies was dermatitis acneiform [10]. This new combination, if validated, will be most probably a new therapeutic option after first-line treatment in *BRAF*-mutated colorectal cancers.

Next to toxicity, the major limiting factor of FOLFOXIRI and bevacizumab is the lack of hypothetical second-line treatment due to the exhaustion of all possibilities in first line. The combination of multiple molecular targeted therapies might be considered a possible

second-line treatment. It is interesting also to explore the role of checkpoint inhibitors in this subgroup of patients, knowing that an important number of patients with *BRAF* mutation are deficient mismatch repair patients, so potentially responders to anti-PD-1 agents. In addition, anti-PD-1 may also be promising agent by extrapolation of the results in melanoma, if evaluated in combination with anti-*BRAF* and anti-MEK agents in *BRAF*-mutated mismatch repair proficient or deficient patients.

Finally, *BRAF*-mutated colorectal cancers represent a new challenge for oncologists, because they are usually aggressive tumors with poor prognosis. It seems that allied therapies FOLFOXIRI and bevacizumab or anti-EGFR/anti-*BRAF*/anti-MEK will represent a new paradigm in the management of these tumors to counteract their resistance to treatment. The design of new trials in colorectal cancers should take into consideration the molecular distribution, to present new possible therapeutic options in these subgroups. Basket trials can be considered an interesting trial design for the evaluation of various targeted therapies in *BRAF*-mutated tumors in different localizations, particularly in colorectal cancers where new therapeutic modalities are necessary to present better results.

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