EUR. J. ONCOL., vol. 19, Suppl n. 1, pp. 36-39, 2014

The Challenge of anti-EGFR therapy-rechallenge in management of metastatic colorectal cancer

Daniele Santini, Marco Imperatori, Bruno Vincenzi, Giuseppe Tonini
Department of Medical Oncology, University Campus Bio-Medico, Rome, Italy

Treatment of metastatic colorectal cancer (mCRC) has undergone several changes thanks to the introduction of targeted therapies inhibiting several disregulatory pathways (1).

Epidermal growth factor receptor (EGFR), a tyrosine kinase receptor belonging to the ErbB family, is overexpressed in 25%-80% of CRCs and plays a major role in its pathogenesis (2) and many clinical trials proved the therapeutic efficacy of antibodies targeting EGFR (cetuximab and panitumumab) in the treatment of CRC patients (3). Therefore, the relatively recent introduction of those anti-EGFR antibodies, combined with standard chemotherapy, allowed to reach the median overall survival of 23-24 months.

Moreover, the median overall response rate to cetuximab or panitumumab based regimens is less than 30%, and several mechanisms of primary resistance to inhibition of EGFR pathway have been studied.

Retrospective and prospective analysis showed that early mutations of Kirsten RAt Sarcoma viral oncogene homologue (K-RAS) gene, occurring in 35-45% of CRC, are associated with primary resistance to anti-EGFR therapy (4-21). Although previous clinical trials have indicated that patients harboring KRAS mutations in codons 12 and 13 are non-responsive to the EGFR-targeted therapy, other analysis showed that some wild-type patients still fail to respond (22) and downstream mutations such as in BRAF, PIK3CA NRAS and rare K-Ras mutations have been investigated (23-29).

Cetuximab is currently approved in Europe as a first line treatment of KRAS WT mCRC, in combination with standard chemotherapy, as second line treatment in combination with irinotecan-based chemotherapy, or as monotherapy in irinotecan or oxaliplatin refractory patients ; while panitumumab is approved for treatment of RAS WT mCRC as first line therapy in combination with FOLFOX, as a second line in combination with FOLFIRI and as a monotherapy in irinotecan and oxaliplatin-refractory patients (30).

But the improvement in management of mCRC patients due to introduction of anti-EGFR and other targeted therapies led to many outstanding issues: 1) there is a significant number of patients progressing beyond the third or fourth line of treatment still suitable for further therapy when enrolment into clinical trial is not possible; 2) Prolonged intensive treatment is burdened from the high risk of cumulative toxicity, worsening in quality of life and a not well defined possibility of early gaining of acquired resistance.

In this sense, rechallenge of an anti-EGFR, defined as reintroduction, after an intervening treatment, of the same therapy to which tumor has already proved to be resistant, could be a new approach for those heavily pretreated patients based on some important preclinical and clinical evidences.

In fact one study evaluated the variation of circulating tumor DNA (ctDNA) in serum of 24 patient receiving single-agent therapy with panitumumab. KRAS mutations were recorded in 38% of cases between 5-6 months following treatment and mathe-

matical modelling indicated that mutations were present in expanded subclones before the initiation of treatment. These results suggest that the selection and emergence of KRAS mutations is a possible mechanism of secondary acquired resistance to EGFR-inhibition (31). Consistently, another small study showed that point mutations of KRAS are casually associated with the onset of acquired resistance to anti-EGFR therapy. In fact analysis of metastasis from ten patients who developed resistance to cetuximab or panitumumab showed the emergence of KRAS mutant alleles were detectable in the blood months before the radiographic evidence of disease progression, and the in vitro model support the hypothesis of continuing mutagenesis (not only involving RAS gene, but also in B-RAF, PI3KCA genes) under the pressure of anti-EGFR therapy (32).

These studies represent an important evidence about the possibility of secondary acquisition of KRAS mutations due to the intensive anti-EGFR-based treatment and could support the strategy of rechallenge.

We can speculate that an interval therapy after first progression to the anti-EGFR therapy could restore a partial sensitivity of tumor to the rechallenge by promoting the re-expansion of RAS wild-type clones, which will constitute the major part of the tumor mass at the time of a following progression of disease. At that time, the readministration of anti-EGFR therapy may then determine a further disease response. Moreover an interval therapy based on a different treatment, which is not influenced by KRAS status or is more efficacious in KRAS mutated CRC, could facilitate the re-emersion of wt clones.

In fact, an in vitro model suggested that KRAS mutated cell lines are more sensitive to Oxaliplatin (33). Consistently, a retrospective study evaluating K-Ras status in 90 patients treated with FOLFOX-6 as first-line or second-line treatment showing that PFS was longer in mutated K-Ras population than in wt KRAS patients (10 vs 8 months, respectively; p=0.001) (34).

Another multicenter phase II prospective study evaluated the activity of a rechallenge with a cetuximab-based therapy in 39 patients who first had a clinical benefit after a line of cetuximab plus irinotecan-based therapy, then a disease progression for which received a new line of chemotherapy and finally, after a further progression of disease, were re-treated with the same cetuximab plus irinotecan based therapy. Overall response rate (RR) was 53.8% with 19 partial responses (48.7%) and 2 complete responses (5.1%). The median time to progression (TTP) was 6.6 months, stable disease (SD) was obtained in 35.9% of patients and progression in 10.2% of cases; and 18 patients showed the same type of response (SD, partial response or complete response) during cetuximab retreatment when compared with the response obtained during the first cetuximab-based therapy. Then stable disease lasting at least 6 months and partial response during the first cetuximab-based therapy have been demonstrated to predict clinical benefit after cetuximab retreatment (35).

Conversely, a phase II prospective study including twenty patients treated with panitumumab after progression on prior cetuximab-based therapy did not show any response being stable disease (no progression for at least two cycles) the best response in 45% of patients (36). But no interval therapy or treatment holiday were permitted between cetuximab and panitumumab administration and it is not possible to know if primary refractory patients to anti-EGFR were enrolled (N-RAS and BRAF status were not evaluated) and data about response to prior cetuximab-based therapy were not available.

Therefore anti-EGFR rechallenge could be a valid therapeutic option in management of mCRC and should be investigated in randomized prospective trial enrolling a selected population of mCRC patients. This selection should be based on different reasonable factors: all-RAS and BRAF wt status, best response to prior treatment before progression (prolonged stable disease, partial response or complete response), residual toxicity and duration of treatment holiday.

References

1. Jass JR. Colorectal cancer: a multipathway disease. Critical Reviews in Oncogenesis 2006; 12: 273-87.
2. Ciardiello F, Tortora G. Drug therapy: EGFR antagonists in cancer treatment. NEJM 2008; 358: 1160-74.

3. Reynolds NA. Wagstaff AJ. Cetuximab. In the treatment of metastatic colorectal cancer. Drugs 2004; 64: 109-18.
4. Cunningham D, Humblet Y, Siena S, *et al*. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. NEJM 2004; 351: 337-45.
5. Karapetis CS, Khambata-Ford S, Jonker DJ, *et al*. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. NEJM 2008; 359 (17): 1757-65.
6. Boerner JL. Role of Src family kinases in acquired resistance to EGFR therapies in cancer. Cancer Biol Ther 2009; 8: 704-6.
7. Wheeler DL, Iida M, Kruser TJ, *et al*. Epidermal growth factor receptor cooperates with Src family kinases in acquired resistance to cetuximab. Cancer Biol Ther 2009; 8: 696-703.
8. Perkins GLA, Ramacci C, Meatchi T, *et al*. Additional value of EGFR downstream signaling phosphoprotein expression to KRAS status for response to anti-EGFR antibodies in colorectal cancer. Int J Cancer 2010; 127: 1321-31.
9. Sartore-Bianchi A, Martini M, Molinari F, *et al*. PIK3CA mutations in colorectal cancer are associated with clinical resistance to EGFR-targeted monoclonal antibodies. Cancer Res 2009; 69: 1851-7.
10. Li C, Iida M, Dunn EF, *et al*. Nuclear EGFR contributes to acquired resistance to cetuximab. Oncogene 2009; 28: 3801-13.
11. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, *et al*. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res 2007; 67: 2643-8
12. Samuels Y, Wang Z, Bardelli A, *et al*. High frequency of mutations of the PIK3CA gene in human cancers. Science 2004; 304: 554.
13. Perrone F, Lampis A, Orsenigo M, *et al*. PI3KCA/PTEN deregulation contributes to impaired responses to cetuximab in metastatic colorectal cancer patients. Ann Oncol 2009; 20: 84-90.
14. Jhawer M, Goel S, Wilson A, *et al*. PIK3CA mutation/PTEN expression status predicts response of colon cancer cells to the epidermal growth factor receptor inhibitor cetuximab. Cancer Res 2008; 68: 1953-61.
15. Bouali S, Chrétien AS, Ramacci C, *et al*. PTEN expression controls cellular response to cetuximab by mediating PI3K/AKT and RAS/RAF/MAPK downstream signaling in KRAS wild-type, hormone refractory prostate cancer cells. Oncol Rep 2009; 21: 731-5.
16. Laurent-Puig P, Cayre A, Manceau G, *et al*. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. J Clin Oncol 2009; 27: 5924-30.
17. Frattini M, Saletti P, Romagnani E, *et al*. PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients. Br J Cancer 2007; 97: 1139-45.
18. Normanno N, Tejpar S, Morgillo F, *et al*. Implications for KRAS status and EGFR-targeted therapies in metastatic CRC.Nat Rev Clin Oncol 2009; 6: 519-27.
19. De Roock W, Piessevaux H, De Schutter J, *et al*. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 2008; 19: 508-15.
20. Khambata-Ford S, Garrett CR, Meropol NJ, *et al*. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007; 25: 230-7.
21. Van Cutsem E, Köhne CH, Láng I, *et al*. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011; 29: 2011-9.
22. Allegra CJ, Jessup JM, Somerfield MR, *et al*. American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol 2009; 27: 2091-6.
23. André T, Blons H, Mabro M, *et al*; GERCOR. Panitumumab combined with irinotecan for patients with KRAS wild-type metastatic colorectal cancer refractory to standard chemotherapy: a GERCOR efficacy, tolerance, and translational molecular study. Ann Oncol 2013; 24: 412-9.
24. Yinchen Shen, Jianfei Wang, Xiaohong Han, *et al*. The Genetic Profiling of KRAS, BRAF, PIK3CA, NRAS Mutations in Colorectal Cancer Characteristics and Personalized Medicine PLoS One 2013; 8: e81628.
25. Douillard JY, Oliner KS, Siena S, *et al*. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013; 369: 1023-34.
26. Di Nicolantonio F, Martini M, Molinari F, *et al*. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008; 26: 5705-12
27. Perrone F, Lampis A, Orsenigo M, *et al*. PI3KCA/PTEN deregulation contributes to impaired responses to cetuximab in metastatic colorectal cancer patients. Ann Oncol 2009; 20: 84-90.
28. Prenen H, De Schutter J, Jacobs B, *et al*. PIK3CA mutations are not a major determinant of resistance to the epidermal growth factor receptor inhibitor cetuximab in metastatic colorectal cancer. Clin Cancer Res 2009; 15: 3184-8.
29. Seymour MT, Brown SR, Middleton G, *et al*. Panitumumab and irinotecan versus irinotecan alone for patients with *KRAS* wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. Lancet Oncol; 14: 749-59.
30. www.ema.europa.eu/ema
31. Diaz LA Jr, Williams RT, Wu J, Kinde I, *et al*. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. Nature 2012; 486: 537-40.

32. Misale S, Yaeger R, Hobor S, *et al*. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. Nature 2012; 28; 486: 532-6.
33. Orlandi A, Di Salvatore M, Basso M, *et al*. ERCC1, KRAS mutation, and oxaliplatin sensitivity in colorectal cancer: Old dogs and new tricks. Gastrointestinal Cancers Symposium 2012, abstract n. 489.
34. Strippoli A, Basso M, Orlandi A, *et al*. KRAS mutational status affects oxaliplatin-based chemotherapy independently from basal mRNA ERCC-1 expression in metastatic colorectal cancer patients. British Journal of Cancer 2013; 108: 115-20.
35. Santini D, Vincenzi B, Addeo R, *et al*. Cetuximab rechallenge in metastatic colorectal cancer patients: how to come away from acquired resistance? Ann Oncol 2012; 23: 2313-8.
36. Wadlow RC, Hezel AF, Abrams TA, *et al*. Panitumumab in Patients with KRAS Wild-Type Colorectal Cancer after Progression on Cetuximab. Oncologist 2012; 17: 14-e35.