Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis.

De Roock W, Claes B, Bernasconi D, De Schutter J, Biesmans B, Fountzilas G, Kalogeras KT, Kotoula V, Papamichael D, Laurent-Puig P, Penault-Llorca F, Rougier P, Vincenzi B, Santini D, Tonini G, Cappuzzo F, Frattini M, Molinari F, Saletti P, De Dosso S, Martini M, Bardelli A, Siena S, Sartore-Bianchi A, Tabernero J, Macarulla T, Di Fiore F, Gangloff AO, Ciardiello F, Pfeiffer P, Qvortrup C, Hansen TP, Van Cutsem E, Piessevaux H, Lambrechts D, Delorenzi M, Tejpar S.

Source

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Abstract

BACKGROUND:

Following the discovery that mutant KRAS is associated with resistance to anti-epidermal growth factor receptor (EGFR) antibodies, the tumours of patients with metastatic colorectal cancer are now profiled for seven KRAS mutations before receiving cetuximab or panitumumab. However, most patients with KRAS wild-type tumours still do not respond. We studied the effect of other downstream mutations on the efficacy of cetuximab in, to our knowledge, the largest cohort to date of patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab plus chemotherapy in the pre-KRAS selection era.

METHODS:

1022 tumour DNA samples (73 from fresh-frozen and 949 from formalin-fixed, paraffin-embedded tissue) from patients treated with cetuximab between 2001 and 2008 were gathered from 11 centres in seven European countries. 773 primary tumour samples had sufficient quality DNA and were included in mutation frequency analyses; mass spectrometry genotyping of tumour samples for KRAS, BRAF, NRAS, and PIK3CA was done centrally. We analysed objective response, progression-free survival (PFS), and overall survival in molecularly defined subgroups of the 649 chemotherapy-refractory patients treated with cetuximab plus chemotherapy.

FINDINGS:

40.0% (299/747) of the tumours harboured a KRAS mutation, 14.5% (108/743) harboured a PIK3CA mutation (of which 68.5% [74/108] were located in exon 9 and 20.4% [22/108] in exon 20), 4.7% (36/761) harboured a BRAF mutation, and 2.6% (17/644) harboured an NRAS mutation. KRAS mutants did not derive benefit compared with wild types, with a response rate of 6.7% (17/253) versus 35.8% (126/352; odds ratio [OR] 0.13, 95% CI 0.07-0.22; p<0.0001), a median PFS of 12 weeks versus 24 weeks (hazard ratio [HR] 1.98, 1.66-2.36; p<0.0001), and a median overall survival of 32 weeks versus 50 weeks (1.75, 1.47-2.09; p<0.0001). In KRAS wild types, carriers of BRAF and NRAS mutations had a significantly lower response rate than did BRAF and NRAS wild types, with a response rate of 8.3% (2/24) in carriers of BRAF mutations versus 38.0% in BRAF wild types (124/326; OR 0.15, 95% CI 0.02-0.51; p=0.0012); and 7.7% (1/13) in carriers of NRAS mutations versus 38.1% in NRAS wild types (110/289; OR 0.14, 0.007-0.70; p=0.013). PIK3CA exon 9 mutations had no effect, whereas exon 20 mutations were associated with a worse outcome compared with wild types, with a response rate of 0.0% (0/9) versus 36.8% (121/329; OR 0.00, 0.00-0.89; p=0.029), a median PFS of 11.5 weeks versus 24 weeks (HR 2.52, 1.33-4.78; p=0.013),

and a median overall survival of 34 weeks versus 51 weeks (3.29, 1.60-6.74; p=0.0057). Multivariate analysis and conditional inference trees confirmed that, if KRAS is not mutated, assessing BRAF, NRAS, and PIK3CA exon 20 mutations (in that order) gives additional information about outcome. Objective response rates in our series were 24.4% in the unselected population, 36.3% in the KRAS wild-type selected population, and 41.2% in the KRAS, BRAF, NRAS, and PIK3CA exon 20 wild-type population.

INTERPRETATION:

While confirming the negative effect of KRAS mutations on outcome after cetuximab, we show that BRAF, NRAS, and PIK3CA exon 20 mutations are significantly associated with a low response rate. Objective response rates could be improved by additional genotyping of BRAF, NRAS, and PIK3CA exon 20 mutations in a KRAS wild-type population.

Comment in

- Lancet Oncol. 2010 Nov;11(11):1020-1.
- Lancet Oncol. 2010 Aug;11(8):706-7.
- Nat Rev Clin Oncol. 2010 Oct;7(10):551.