Colorectal Oncology
RESEARCH REVIEW™

Making Education Easy

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In this issue:

Abbreviations used in this issue

CAPOX = capecitabine, oxaliplatin
CRC = colorectal cancer
EGFR = epidermal growth factor receptor
ESMO = European Society for Medical Oncology
FOLFIRI = folinic acid, fluorouracil and irinotecan
FOLFOX = folinic acid, fluorouracil and oxaliplatin
HR = hazard ratio
KRAS = Kirsten Rat Sarcoma
mAb = monoclonal antibody
mCRC = metastatic colorectal cancer
NCCTN = National Cancer Institute National Cancer Clinical Trials Network
OS = overall survival
PFS = progression-free survival
SEER = Surveillance, Epidemiology and End Results
VEGF = vascular endothelial growth factor

Welcome to this issue of Colorectal Oncology Research Review.

According to recent paper published in the European Journal of Cancer, genotyping of the *RSPO2 rs555008* polymorphism may help to select metastatic colorectal cancer patients who will derive the most benefit from FOLFIRI/bevacizumab. The New EPOC study suggests that cetuximab should not be added to chemotherapy in the perioperative setting of operable colorectal liver metastasis. Other studies involving patients with mCRC investigate chemotherapy with or without cetuximab for resectable colorectal liver metastasis, maintenance strategies, cetuximab versus bevacizumab, and aflibercept plus fluorouracil, leucovorin, and irinotecan.

We hope you find the papers in this issue useful in your practice and welcome your comments and feedback.

Kind regards

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A polymorphism within the R-spondin 2 gene predicts outcome in metastatic colorectal cancer patients treated with FOLFIRI/bevacizumab: Data from FIRE-3 and TRIBE trials

Authors: Berger MD et al.

Summary: This analysis of data from the randomised phase III FIRE-3 and TRIBE trials examined whether R-spondin gene variations (6 functional single-nucleotide polymorphisms [SNPs] in R-spondin 1-3 genes) were predictive of outcome in 773 patients with metastatic colorectal cancer (mCRC) receiving FOLFIRI and bevacizumab. Overall survival (OS) was longer among *RAS* wild-type patients with any G allele of the *RSPO2 rs555008* SNP versus those with a TT genotype in both FIRE-3 (29.0 vs 23.6 months; p = 0.009) and TRIBE (37.8 vs 19.4 months, p = 0.021) cohorts, and among *KRAS* wild-type vs TT patients (FIRE-3 28.4 vs 22.3 months; p = 0.011; TRIBE 36.0 vs 23.3 months; p = 0.046). G allele carriers with *KRAS* and *RAS* mutant tumours had shorter progression-free survival than TT genotype carriers, and the results were stronger among *KRAS* patients in both FIRE-3 and TRIBE cohorts (8.1 vs 11.2 months; p = 0.023 and 8.7 vs 10.3 months; p = 0.009).

Comment: This analysis is yet another attempt at finding a useful predictive molecular marker to help the decisions about treatment with antiangiogenic targeted agents. Head-to-head comparisons of bevacizumab and cetuximab have shown comparable outcomes in the first-line settings. There has been a considerable effort put into finding the proper sequencing of VEGF and EGFR inhibitors. Bevacizumab-induced hypoxia most likely leads to the poor performance of anti-EGFR mAb in second-line treatment. Furthermore, anti-EGFR mAb does not show an advantage in survival outcomes compared to continuation of bevacizumab in second-line treatment. We can only speculate that first-line anti-EGFR followed by anti-VEGF is the best sequence in patients with left-sided tumours. Continued use of bevacizumab after progression on first-line bevacizumab is applicable for patients with right-sided tumours, and anti-EGFR mAbs may be more appropriate after a third-line chemotherapy regimen or regorafenib.

Reference: Eur J Cancer. 2020;131:89-97
Abstract

Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis (New EPOC): Long-term results of a multicentre, randomised, controlled, phase 3 trial

Authors: Bridgewater JA et al.

Summary: This analysis of the multicentre, open-label, randomised, controlled, phase 3 New EPOC trial aimed to assess the effect on OS in patients with KRAS wild-type resectable or suboptimally resectable colorectal liver metastasis receiving cetuximab plus chemotherapy (n = 129) versus chemotherapy alone (n = 128); chemotherapy consisted of FOLFOX, FOLFIRI or CAPOX. After a median follow-up of 66.7 months, the median progression-free survival (PFS) did not differ between chemotherapy alone (22.2 months; 95% CI 18.3-26.8) versus chemotherapy plus cetuximab (15.5 months; 95% CI 13.8-19.0; HR 1.17; 95% CI 0.87-1.56). Median OS was 81.0 months versus 55.4 months for chemotherapy alone versus chemotherapy plus cetuximab (HR 1.45; 95% CI 1.02-2.05; p = 0.036). Secondary outcomes of preoperative response or pathological resection status did not differ between groups. Possibly treatment-related deaths occurred in 1 chemotherapy alone and 4 chemotherapy plus cetuximab recipients. The most common grade 3-4 adverse events were neutrophil count decrease (19% vs 15%), diarrhoea (10% vs 10%), skin rash (1% vs 16%), thromboembolic events (7% vs 8%), lethargy (7% vs 7%), oral mucositis (2% vs 10%), pain (4% vs 4%), vomiting (5% vs 5%) and peripheral neuropathy (6% vs 4%) in the chemotherapy alone and chemotherapy plus cetuximab groups, respectively.

Comment: The EPOC (EORTC 40983) study showed 7% improvement in PFS with the addition of perioperative FOLFOX chemotherapy to surgical resection of colorectal liver metastases. In this New EPOC study in patients with borderline resectable and resectable colorectal liver metastases cetuximab was added to the chemotherapy backbone (FOLFOX 69%, CAPOX 21%, FOLFIRI 10%) and compared to the same chemotherapy given for 3 months prior to and 3 months post-surgery. Even though PFS was still in favour of chemotherapy alone, the difference was no longer statistically significant in this final analysis. However, OS was significantly worse in patients receiving cetuximab and chemotherapy and particularly the ones with better prognosis (well differentiated tumours, less postive nodes and <4 liver metastases). More patients in cetuximab group did not undergo planned surgery due to progressive disease (20% vs 52%). The HR point estimate for detriment with cetuximab in the all RAS/RAF wild-type population was almost identical to that in the whole trial population. It seems that the detriment with cetuximab was limited to the patients with high expression of micro RNA (miR-31-3p) in the primary tumours. There has also been some speculation about a negative interaction between oxaliplatin and cetuximab based on the studies that didn't show benefit in wild-type all *RAS/BRAF* tumours when cetuximab was added to the oxaliplatin-based chemotherapy (COIN and Norwegian studies) compared to the positive studies combining irinotecan-based chemotherapy with cetuximab. In the pre-planned subset analysis of this study the detriment was obvious in patients receiving oxaliplatin-based chemotherapy, but not in the ones receiving FOLFIRI (10%) with cetuximab. In the advanced disease setting, right-sided metastatic colon cancer has been reported to be less responsive to EGFR inhibition. Similarly, in this trial, survival of patients with liver metastases from right-sided cancers was affected more than that of patients with left-sided cancers by the addition of cetuximab.

Reference: Lancet Oncol. 2020;21(3):398-411
Abstract

TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: An investigator-initiated, open-label, randomised, phase 2 trial

Authors: Pfeiffer P et al.

Summary: This Danish investigator-initiated, open-label, randomised, phase II trial compared the efficacy of TAS-102 (trifluridine-tipiracil) plus bevacizumab (n = 46) versus TAS-102 alone (n = 47) in patients receiving refractory therapy for mCRC. Over a median follow-up of 10.0 months. median PFS was 2.6 months (95% CI 1.6-3.5) with TAS-102 alone versus 4.6 months (95% CI 3.5-6.5) for TAS-102 plus bevacizumab (HR 0.45; 95% CI 0.29-0.72; p = 0.0015). The most frequent grade ≥3 adverse event was neutropenia (38% for TAS-102 alone vs 67% for TAS-102 plus bevacizumab). Serious adverse events occurred in 45% vs 41%.

Comment: This is yet another trial showing the benefit in adding bevacizumab to chemotherapy, this time in the later line of treatment of mCRC patients. The gain in PFS benefit is similar to the one described in other trials that added bevacizumab to the earlier lines of chemotherapy. This confirms that inhibition of angiogenesis in combination with chemotherapy is a valid concept and unlike EGFR inhibitors it can be maintained across different lines of chemotherapy and irrespective of the sidedness of the primary tumour. It would be worthwhile knowing the amount of cumulative benefit in using different antiangiogenic agents in multiple lines of treatment, but the design of such a study would be very challenging.

Reference: Lancet Oncol. 2020;21(3):412-420
Abstract

Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2)

Authors: Cremolini C et al.

Summary: The open label, randomised, phase III TRIBE2 study compared a pre-planned strategy of upfront FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan) plus bevacizumab followed by reintroduction of the same regimen after disease progression (n = 340) versus mFOLFOX6 (fluorouracil, leucovorin, oxaliplatin) and FOLFIRI (irinotecan, leucovorin, fluorouracil) after progression, both in combination with bevacizumab (n = 339). After a median follow-up of 35.9 months, the median PFS 2 (time from randomisation to disease progression after first disease progression or death) was 19.2 months (95% CI 17.3-21.4) for FOLFOXIRI plus bevacizumab and 16.4 months (95% CI 15.1-17.5) for mFOLFOX6/FOLFIRI plus bevacizumab (HR 0.74; 95% CI 0.63-0.88; p = 0.0005). During first-line treatment, the most frequent all-cause grade 3-4 events were diarrhoea (17% vs 5%), neutropenia (50% vs 21%), and arterial hypertension (7% vs 10%) for FOLFOXIRI plus bevacizumab versus mFOLFOX6/FOLFIRI plus bevacizumab. Serious adverse events occurred in 25% FOLFOXIRI plus bevacizumab recipients versus 17% of mFOLFOX6/FOLFIRI plus bevacizumab recipients; treatment-related deaths occurred in 8 vs 4 patients. After first disease progression there were no differences in incidence of grade 3-4 adverse events, with the exception of neurotoxicity which occurred only in FOLFOXIRI plus bevacizumab recipients (5%). Serious adverse events after disease progression occurred in 15% vs 12% of FOLFOXIRI plus bevacizumab versus mFOLFOX6/FOLFIRI plus bevacizumab recipients; treatment-related deaths after first disease progression occurred in 3 versus 4 patients.

Comment: This large randomised trial compared the experimental stop-and-go policy with FOLFOXIRI triplet to the standard sequential treatment with FOLFOX and FOLFIRI doublets. In both arms the patients were given a limited number of cycles of the initial chemotherapy followed by the same maintenance regimen with infusional 5-fluorouracil/leucovorin and bevacizumab. One could argue that the experimental arm did better due to patients receiving more chemotherapy in the initial induction phase. Therefore, it would have been beneficial to not only know the PFS 2 but also the PFS 1 interval (from randomisation to first disease progression) or interval between the first disease progression and the time at second disease progression. More chemotherapy resulted in slightly better outcome, but at the expense of more toxicity with a concerning number of treatment-related deaths associated with that strategy.

Reference: Lancet Oncol. 2020;21(4):497-507
Abstract

The role of maintenance strategies in metastatic colorectal cancer: A systematic review and network meta-analysis of randomized clinical trials

Authors: Sonbol MB et al.

Summary: This meta-analysis used data from 12 randomised trials (n = 5540) to determine the comparative effectiveness of different treatment strategies after first-line induction therapy in patients (23-85 years of age; 64.4 % male) with previously untreated mCRC. Network meta-analysis indicated no benefit of continuing full cytotoxic chemotherapy until progression compared with observation for either PFS (HR 0.71; 95% CI 0.46-1.09) or OS (HR 0.95; 95% CI 0.85-1.07). Maintenance therapy with bevacizumab, fluoropyrimidine, or both had a PFS benefit over observation (HR 0.58; 95% CI 0.43-0.77), but there was no OS benefit (HR 0.91; 95% CI 0.83-1.01). All maintenance strategies were beneficial versus observation. Surface under cumulative ranking (SUCRA) analysis, suggested that maintenance treatment with fluoropyrimidine with or without bevacizumab had the highest likelihood of achieving improved PFS (fluoropyrimidine 67.1%; fluoropyrimidine + bevacizumab 99.8%; bevacizumab 36.5%) and OS (fluoropyrimidine 81.3%; fluoropyrimidine + bevacizumab 73.2%; bevacizumab 32.6%).

Comment: Previously reported studies on stop and go and maintenance treatment showed conflicting results. This meta-analysis showed that scheduled chemotherapy treatment breaks are not detrimental for the outcomes. However, continuation with de-escalated 5 fluorouracil-based chemotherapy or introduction of bevacizumab in the maintenance regimen increases the likelihood of longer PFS but without a statistically significant impact on OS. The current guidelines (ESMO, Asian and NCCN) recommend maintenance treatment with a fluoropyrimidine and bevacizumab after a limited number of cycles of first-line oxaliplatin-based chemotherapy to reduce the intensity of oxaliplatin-induced neurotoxicity. If FOLFIRI is used first line, there is no limitation in the number of cycles, but treatment breaks are encouraged in the patients with more indolent and slower growing tumours.

Reference: JAMA Oncol. 2019;6(3):e194489
Abstract

The efficacy and safety of panitumumab supplementation for colorectal cancer: A meta-analysis of randomized controlled studies

Authors: Wang C et al.

Summary: This meta-analysis of 5 randomised controlled trials examined the influence of panitumumab supplementation on the treatment of colorectal cancer. Overall, panitumumab supplementation was associated with an increase in objective response over control for wild-type (WT) *KRAS* (RR 1.70; 95% CI 1.07-2.69; p = 0.03), but not mutant *KRAS* (RR 0.92; 95% CI 0.79-1.08). In addition, it had no effect on overall objective response (RR 1.35; 95% CI 1.00-1.83), progressive disease for WT *KRAS* (RR 0.94; 95% CI 0.85-1.02), overall mortality (RR 0.86; 95% CI 0.69-1.08), or mortality for WT *KRAS* (RR 0.94; 95% CI 0.84-1.05). Grade 3-4 adverse events were higher in panitumumab than control recipients (RR 1.17; 95% CI 1.08-1.27; p = 0.0001).

Comment: The individual randomised studies have shown the beneficial effect of the addition of panitumumab (fully human monoclonal antibody to EGFR) to first- and second-line chemotherapy. Since there have also been some negative studies, this meta-analysis is an attempt at compiling the evidence. It showed a significant increase in overall response rates in the treatment of *KRAS* WT mCRC but not the tumours with unknown or mutant *KRAS*. Unfortunately, the survival analysis could not be performed due to heterogeneity of the studies, which illustrates the futility of meta-analyses using published and not individual patient data.

Reference: Medicine (Baltimore) 2020;99(11):e19210
Abstract

Cetuximab versus bevacizumab in metastatic colorectal cancer: A comparative effectiveness study

Authors: Marques RP et al.

Summary: This retrospective multi-cohort study compared clinical outcomes for cetuximab versus bevacizumab in 311 patients with mCRC. Analysis of first- and second-line cohorts found no differences between bevacizumab and cetuximab for PFS in either first-line (HR 0.85; 95% CI 0.64-1.13) or second-line (HR 1.16; 95% CI 0.74-1.83) use, nor any difference in OS for either first-line (HR 0.83; 95% CI 0.61-1.15) or second-line (HR 0.88; 95% CI 0.56-1.38) use. Subgroup analyses of first-line therapy indicated a difference favouring bevacizumab for right-sided tumours for both PFS (HR 0.52; 95% CI 0.29-0.93; p = 0.025) and OS (HR 0.60; 95% CI 0.32-1.12; p = 0.11), but not for left-sided tumours in either PFS (HR 1.04; 95% CI 0.75-1.46) nor OS (HR 0.94; 95% CI 0.65-1.36). There was also no difference for *RAS/KRAS* wild-type tumours for PFS (HR 0.91; 95% CI 0.60-1.40) nor OS (HR 0.79; 95% CI 0.50-1.25). With respect to response rates, bevacizumab performed substantially better only in a subgroup of patients with right-sided primary tumours.

Comment: This analysis adds to the evidence that bevacizumab is a more suitable partner to chemotherapy than cetuximab in right-sided mCRC. Even though the regulatory bodies would like to see randomised trials addressing the sidedness as a predictive factor in decision about the targeted treatments, the reality is that they are unlikely to happen. Therefore, similar reports are more than welcome. There is a huge expectation that further molecular analyses should clarify this issue in the near future.

Reference: J Cancer Res Clin Oncol. 2020;146(5):1321-1334
Abstract

Circulating tumor DNA is capable of monitoring the therapeutic response and resistance in advanced colorectal cancer patients undergoing combined target and chemotherapy

Authors: Cao H et al.

Summary: This study examined plasma circulating tumour DNA (ctDNA) mutational changes (605-gene next-generation sequencing panel) in 43 patients with advanced colorectal cancer undergoing first-line therapy with bevacizumab and cetuximab combined with chemotherapy. Baseline genes with the highest mutation frequency were *TP53* (74%), *APC* (58%), *KRAS* (40%), *SYNE1* (33%), *LRP1B* (23%), *TOP1* (23%) and *PIK3CA* (21%). Paired plasma and tissue samples from 29 patients established overall mutation consistency of 54.6%; the most consistent mutations were *TP53* (81%), *APC* (67%) and *KRAS* (42%). Following first-line therapy, there was an alleviation of mutational burden in *BRAF*, *KRAS*, *AMER1* and other major driving genes. *KRAS* and *TP53* mutations appeared to be reduced more than wild-type and the change of plasma mutation status was consistent with tissue tumour burden and correlated with disease progression.

Comment: This study pointed out the dynamic nature of cancer gene mutations during the course of advanced colorectal cancer. The impact of chemotherapy and targeted treatments is also important and monitoring ctDNA is becoming a significant tool in the development of personalised cancer care. The caveat of these studies is the use of different technologies and methods lowering the specificity and sensitivity of the tests and reproducibility in different laboratories.

Reference: Front Oncol. 2020;10:466
Abstract

Population-based SEER analysis of survival in colorectal cancer patients with or without resection of lung and liver metastases

Authors: Siebenhüner AR et al.

Summary: This population-based analysis of data from the Surveillance, Epidemiology and End Results (SEER) database aimed to determine the effect on survival of resection of liver only, lung only and liver and lung metastases in 10,325 patients with mCRC and resected primary tumour. Most patients had liver-only metastases (79.4%), 7.8% had lung-only metastases and 12.8% had lung and liver metastases. Three-year OS was 44.5% versus 27.5% for patients with versus without metastasectomy (HR 0.62; 95% CI 0.58-0.65; $p < 0.001$). In multivariate analysis, cancer-specific survival was improved by metastasectomy for liver metastases (HR 0.72; 95% CI 0.67-0.77; $p < 0.001$), but not for lung metastases (HR 0.84, 95% CI 0.62-1.12) nor combined liver and lung metastases (HR 0.89; 95% CI 0.75-1.06). Similar results were achieved for OS and after adjustment by inverse propensity weighting, near/far matching and propensity score.

Comment: The resection of oligometastatic disease in advanced cancers has been adopted as reasonable practice. Even though randomised trials are lacking, a large number of single or multi-institutional retrospective reports indicate longer term benefits with resection of technically resectable metastatic disease. Most of these reports don't take into account confounding variables such as natural history of the disease or impact of subsequent systemic treatments on survival. Therefore, the results of this analysis using the matched propensity scores and weighted analysis should be better respected in the scientific community. It clearly showed a survival benefit for the resection of liver but not lung secondaries. Survival was also better in left-sided colorectal cancer, patients with node-negative disease, lower grade and T-stage tumours and in younger, married, Caucasian patients who also underwent chemotherapy.

Reference: BMC Cancer. 2020;20(1):246
Abstract

Safety and effectiveness of aflibercept + fluorouracil, leucovorin, and irinotecan (FOLFIRI) for the treatment of patients with metastatic colorectal cancer (mCRC) in current clinical practice: OZONE study

Authors: Chau I et al.

Summary: The prospective, observational, noncomparative safety study (OZONE) examined the use of aflibercept plus FOLFIRI in 766 patients (59.5% male, 94.8% Eastern Cooperative Oncology Group performance status of 0-1) with mCRC after failure of an oxaliplatin-based regimen; 58.6% of patients had prior exposure to bevacizumab. Overall, 68.3% of patients reported ≥1 grade ≥3 treatment-emergent adverse event, with the most frequent being neutropenia, hypertension, diarrhoea and asthenia. Subgroup analyses for age, renal and hepatic status, race or prior anticancer therapy did not identify major differences in safety profile. The median OS was 12.5 months and median PFS was 6.1 months; overall response rate was 16.3%.

Comment: VELOUR was a phase III, randomised, placebo-controlled study investigating aflibercept (VEGF trap) plus FOLFIRI for patients with mCRC progressing on or after an oxaliplatin-based regimen. This post-registration safety study confirmed the findings of the randomised controlled trial showing the benefit for addition of this anti-VEGF agent to FOLFIRI chemotherapy in the unrestricted mCRC patient population. Patients in the OZONE study were older (median 64 years; 48.3% aged ≥65 years) than those in the VELOUR study (median 61 years; 33.5% aged ≥65 years), more patients had neoadjuvant/adjuvant chemotherapy (45.7% vs 26.5%) and prior exposure to bevacizumab (58.6% vs 27.6%), and more patients had >1 line of treatment. Subgroup analysis of the OZONE study did not show major differences in the safety profile according to age, renal and hepatic status, race or prior anticancer therapy, supporting its use in older populations with co-morbidities such as renal and hepatic impairment. However, the treatment with aflibercept favoured the subgroups of patients with no hepatic impairment or no prior use of bevacizumab.

Reference: Cancers (Basel). 2020;12(3):E657
Abstract

Independent commentary by Dr Dragan Damianovich

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