drugs. However, our current health care system does not facilitate a 'learning health care system'. In general, there are no structured clinical data collections of the outcome of off-label use. In the Netherlands, this approach has been incorporated into a 'Drug Rediscovery Protocol' (acronym DRUP) study (ClinicalTrials.gov Identifier: NCT02925234). DRUP serves as a platform where patients can be treated with off-label targeted agents whilst collecting all relevant outcome data. This approach improves access to these off-label drugs, diminishing inequalities in care, ensures robust review of target and treatment selection, and prospectively collects outcome data to be shared with industry, payers and regulatory bodies. This study, initiated in 2016, now has over 26 approved targeted drugs at its disposal. Data from this study led to a pay-for-performance system [10] for nivolumab in patients with MSI-high tumors (no approved drug available in Europe for this indication) whereby the manufacturer provides nivolumab for free during the first 16 weeks of treatment with payer commitment to reimbursement for responding patients. Negative findings are shared with the scientific community in order to prevent repetitive treatments without the outlook of clinical benefit. Several countries are now using similar protocols [e.g. TAPUR (NCT02693535) and CAPTUR (NCT03297606)] which specifically allow data sharing.

In conclusion, while we are grateful for all the novel drugs that have been developed for cancer, we have an obligation to maximize the clinical value for our patients and communities. These dual obligations require commitments to rational off-label use and to structured learning through data collection and sharing in order to identify those approaches that deserve to become licensed indications and to be reimbursed. Importantly, this allows us to distinguish them from those that are inadequately effective to justify licensing or clinical recommendation.

E. G. E. de Vries[1*], N. I. Cherny[2] & E. E. Voest[3,4]
[1]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [2]Department of Medical Oncology, Cancer Pain and Palliative Medicine Service, Shaare Zedek Medical Center, Jerusalem, Israel; [3]Division of Molecular Oncology, The Netherlands Cancer Institute, Amsterdam; [4]Oncode Institute, Amsterdam, The Netherlands
(*E-mail: e.g.e.de.vries@umcg.nl)

Disclosure

EGEdV reports Institutional Financial Support for her advisory role from Daiichi Sankyo, Merck, NSABP, Pfizer, Sanofi, Synthon and Institutional Financial Support for clinical trials or contracted research from Amgen, AstraZeneca, Bayer, Chugai Pharma, CytomX Therapeutics, G1 Therapeutics, Genentech, Nordic Nanovector, Radius Health, Regeneron, Roche, Synthon, all outside the submitted work. EEV is medical director of the executive board of the Netherlands Cancer Institute and as such legally responsible for all contracts with pharma.

References

1. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-approval-new-cancer-treatment-uses-marketed-drug-and-biological-products (12 August 2019, date last accessed).
2. Kalis JA, Pence SJ, Mancini RS et al. Prevalence of off-label use of oral oncolytics at a community cancer center. J Oncol Pract 2015; 11(2): e139–e143.
3. Conti RM, Bernstein AC, Villaflor VM et al. Prevalence of off-label use and spending in 2010 among patent-protected chemotherapies in a population-based cohort of medical oncologists. J Clin Oncol 2013; 31(9): 1134–1139.
4. Wagner J, Marquart J, Ruby J et al. Frequency and level of evidence used in recommendations by the National Comprehensive Cancer Network guidelines beyond approvals of the US Food and Drug Administration: retrospective observational study. BMJ 2018; 360: k668.
5. Kurzrock R, Gurski LA, Carlson RW et al. Level of evidence used in recommendations by the National Comprehensive Cancer Network (NCCN) guidelines beyond Food and Drug Administration approvals. Ann Oncol 2019; 30(10): 1647–1652.
6. www.nccn.org/professionals/physician_gls/categories_of_consensus.aspx (12 August 2019, date last accessed).
7. Mateo J, Chakravarty D, Dienstmann R et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2018; 29(9): 1895–1902.
8. Gyawali B, Kesselheim AS. The promise of ESCAT: a new system for evaluating cancer drug-target pairs. Nat Rev Clin Oncol 2019; 16 (3): 147–148.
9. Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017; 28(10): 2340–2366.
10. van Waalwijk van Doorn-Khosrovani SB, Pisters-van Roy A, van Saase L et al. Personalised reimbursement: a risk-sharing model for biomarker-driven treatment of rare subgroups of cancer patients. Ann Oncol 2019; 30(5): 663–665.

Funding

None declared.

doi:10.1093/annonc/mdz445
Published online 5 November 2019

Is the tumour microenvironment a critical prognostic factor in early-stage colorectal cancer?

The TNM staging system remains the cornerstone of risk assessment in patients with early-stage colorectal cancer (CRC). However, clinical behaviour is diverse within the same stages, making prognostication an imprecise science. Microsatellite instability (MSI) is the only biomarker routinely considered beyond TNM, although a range of major genomic changes is well established, with contradictory evidence in outcome prediction [1, 2]. So what other markers could improve prognostic precision?

CRC heterogeneity has now been comprehensively characterised at the transcriptomic level as between three and six prognostic and potentially predictive subtypes [3–8]. For clinical application, these competing subtypes were integrated into four consensus molecular subtypes (CMS1–4) by the ColoRectal

Cancer Subtyping Consortium [9]. The CMS classification has shown prognostic significance in both the early and advanced settings in multiple cohorts from high-quality clinical trials testing contemporary regimens [10–13]. While CMS2 and CMS3 primarily represent epithelial cancer cell heterogeneity, CMS1 and CMS4 also include cellular components of the tumour microenvironment, mainly immune cells and stromal fibroblasts [9, 10, 14].

The immune microenvironment is known to contribute to CRC patient prognosis [15]. Among tumour microenvironment cells, immune cell infiltrates, specifically cytotoxic T lymphocytes (CytoLym, enriched in CMS1), are associated with better outcomes in early-stage CRC patients [15]. The CMS4 subtype is enriched for cancer-associated fibroblasts (CAFs) and has a poor prognosis [9, 16]. Is it possible that subtype-specific prognosis is driven by the microenvironment?

To address this question and following up on their previous study [1], Dienstmann et al. explored whether tumour microenvironment features such as CytoLym and CAFs are stronger determinants of disease-free survival (DFS) in early-stage CRC patients than the known genomic aberrations (MSI, *BRAF* and *KRAS* mutational status) and CMS subtypes [17]. Their large, retrospective study of several public and private clinically annotated stage II/III CRCs ($n = 2,636$), both untreated ($n = 1,656$) and treated ($n = 980$), evaluated CMS1/4 subtype scores and microenvironment-based (CytoLym and CAF) continuous scores *in silico*. In a multivariable model, clinicopathological (including TNM) and microenvironment features were independent prognostic factors. Clinicopathological variables explained the majority (56%–77%) of variation in DFS, followed by immune stromal infiltrating markers (14%–35%), while only <6% of DFS variation was explained by CMS and genomic factors. Moreover, CAF scores were associated with poor prognosis exclusively in stage III cancers while CytoLym scores were associated with good prognosis specifically in stage II and microsatellite stable cancers. Hence, CMS4 and MSI subtypes (enriched for CAFs and CytoLym, respectively [14, 16]) were not prognostic when these specific microenvironment features were included [17].

This study adds to the evidence that the tumour microenvironment plays a crucial prognostic role in CRC. The authors must be appreciated for their efforts in collecting over 2600 patient samples from public and private (including clinical trial) datasets. Their findings are consistent with previous studies, in particular with the immunohistochemistry assay Immunoscore®, which has been extensively validated in early-stage CRCs [18].

Overall, this represents an excellent summary of the relative contribution of clinicopathological and molecular features in explaining DFS. Validation of these current results in additional, high-quality datasets is recommended, including those in oxaliplatin-treated stage III cancers. However, the study has limitations. Genomic data (MSI and *BRAF* mutation) were missing for a large number of samples, which were instead imputed computationally, although the prevalence of these aberrations was similar to those previously reported [2]. Conversely, all included samples had CytoLym and CAF scores available. This inconsistent availability of data may have biased the statistical analyses. Hence, the results of these exploratory analyses in this study of multiple retrospective cohorts need to be interpreted appropriately.

Age is usually considered a clinical factor when balancing chemotherapy benefit against side-effects [2]. As highlighted by the authors [17], age accounted for a significant proportion of DFS, especially in the untreated (and older) population, who more often experience non-cancer-related deaths. Hence, it is worth considering only CRC-related relapses for DFS.

Sidedness is a known surrogate biomarker of complex CRC biology: while the poor prognosis and reduced response to anti-epidermal growth factor receptor therapy in the right-sided metastatic setting is increasingly recognised, the prognostic role of sidedness in early-stage CRC is less clear [19]. The current study shows that right-sided early-stage (II and III) CRCs have a better DFS than left-sided CRCs irrespective of MSI status (using partially imputed data) [17], similar to previously published results [20]. Nevertheless, this observation requires further validation using well-annotated data to assess whether these observations are generalisable to early CRCs in the real clinical setting.

The MicroCells approach was limited to detecting only a few immune cell types and did not include, for example, T regulatory cells and specific macrophage subsets, which may be important in governing pro- and anti-inflammatory responses in tumours and, therefore, prognosis. Furthermore, the scores for the microenvironment cell types may vary depending on the cell-type markers and computational methods used. It is worth remembering that computational methods require rigorous validation using established immunohistochemistry or similar experimental methods before clinical application. Nevertheless, the association between CytoLym and MSI status suggests that this study included the most relevant microenvironment scores and important immune populations.

This interesting study now prompts the question of what other factors beyond the microenvironment may affect prognosis in patients with early-stage CRCs. Epigenetics, colonic crypt cell types (similar to previously reported [3]), tumour mutational burden, and neoantigens are promising candidates. Whatever the answer, robust and clinically relevant biomarkers and assays are mandatory for effective clinical translation, which may need to be developed in the future based on the current study. Nevertheless, with further validation, these findings will hopefully facilitate our understanding of the relative contributions of cancer cells and the microenvironment in determining prognosis in early-stage CRC patients and refine personalised medicine approaches in the future.

G. Nyamundanda, E. Fontana & A. Sadanandam*
Division of Molecular Pathology, Institute of Cancer Research, London, UK
(*E-mail: anguraj.sadanandam@icr.ac.uk)

Funding

None declared.

Disclosure

AS has ownership interest as an inventor for a patent entitled 'Colorectal cancer classification with differential prognosis and

personalised therapeutic responses' (patent number PCT/IB2013/060416). AS received research funding from Bristol-Myers Squibb, Merck KGaA and Pierre Fabre. All remaining authors have declared no conflicts of interest.

References

1. Dienstmann R, Mason MJ, Sinicrope FA et al. Prediction of overall survival in stage II and III colon cancer beyond TNM system: a retrospective, pooled biomarker study. Ann Oncol 2017; 28(5): 1023–1031.
2. Labianca R, Nordlinger B, Beretta GD et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24(Suppl 6): vi64–72.
3. Sadanandam A, Lyssiotis CA, Homicsko K et al. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. Nat Med 2013; 19(5): 619–625.
4. De Sousa E Melo F, Wang X, Jansen M et al. Poor-prognosis colon cancer is defined by a molecularly distinct subtype and develops from serrated precursor lesions. Nat Med 2013; 19(5): 614–618.
5. Marisa L, de Reyniès A, Duval A et al. Gene expression classification of colon cancer into molecular subtypes: characterization, validation, and prognostic value. PLoS Med 2013; 10(5): e1001453.
6. Roepman P, Schlicker A, Tabernero J et al. Colorectal cancer intrinsic subtypes predict chemotherapy benefit, deficient mismatch repair and epithelial-to-mesenchymal transition. Int J Cancer 2014; 134(3): 552–562.
7. Schlicker A, Beran G, Chresta CM et al. Subtypes of primary colorectal tumors correlate with response to targeted treatment in colorectal cell lines. BMC Med Genomics 2012; 5(1): 1–15.
8. Budinska E, Popovici V, Tejpar S et al. Gene expression patterns unveil a new level of molecular heterogeneity in colorectal cancer. J Pathol 2013; 231(1): 63–76.
9. Guinney J, Dienstmann R, Wang X et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015; 21(11): 1350–1356.
10. Fontana E, Eason K, Homicsko K, Sadanandam A. Molecular classification of colon cancer: perspectives for personalized adjuvant therapy. Curr Colorectal Cancer Rep 2016; 12(6): 296–302.
11. Lenz HJ, Ou FS, Venook AP et al. Impact of consensus molecular subtype on survival in patients with metastatic colorectal cancer: results from CALGB/SWOG 80405 (Alliance). J Clin Oncol 2019; 37(22): 1876–1885.
12. Song N, Pogue-Geile KL, Gavin PG et al. Clinical outcome from oxaliplatin treatment in stage II/III colon cancer according to intrinsic subtypes: secondary analysis of NSABP C-07/NRG oncology randomized clinical trial. JAMA Oncol 2016; 2(9): 1162–1169.
13. Fontana E, Eason K, Cervantes A et al. Context matters-consensus molecular subtypes of colorectal cancer as biomarkers for clinical trials. Ann Oncol 2019; 30(4): 520–527.
14. Dienstmann R, Vermeulen L, Guinney J et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Nat Rev Cancer 2017; 17(2): 79–92.
15. Mlecnik B, Tosolini M, Kirilovsky A et al. Histopathologic-based prognostic factors of colorectal cancers are associated with the state of the local immune reaction. J Clin Oncol 2011; 29(6): 610–618.
16. Calon A, Lonardo E, Berenguer-Llergo A et al. Stromal gene expression defines poor-prognosis subtypes in colorectal cancer. Nat Genet 2015; 47(4): 320–329.
17. Dienstmann R, Villacampa G, Sveen A et al. Relative contribution of clinicopathological variables, genomic markers, transcriptomic subtyping and microenvironment features for outcome prediction in stage II/III colorectal cancer. Ann Oncol 2019; 30(10): 1622–1629.
18. Pages F, Mlecnik B, Marliot F et al. International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. Lancet 2018; 391: 2128–2139.
19. Petrelli F, Tomasello G, Borgonovo K et al. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. JAMA Oncol 2017; 3(2): 211–219.
20. Kennecke HF, Yin Y, Davies JM et al. Prognostic effect of sidedness in early stage versus advanced colon cancer. Health Sci Rep 2018; 1(8): e54.

doi:10.1093/annonc/mdz294
Published online 29 August 2019