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Practice–changing updates in the adjuvant and metastatic setting

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Abstract

2017 has been full of new discoveries that will influence the treatment of colorectal cancer. In the adjuvant setting, 3 months of chemotherapy might now be considered a new standard of care. Various other new treatments and promising biomarkers have also become available that will improve survival outcomes and the quality of life of many patients with metastatic disease.

Colorectal cancer (CRC) is one of the leading causes of cancer death worldwide. In the past decade, numerous exciting advances have been made in the treatment of patients with metastatic disease. In fact, since bevacizumab was approved for patients with metastatic CRC (mCRC) in 2004, a further six agents (both biologic and chemotherapeutic compounds) have become standard-of-care treatments. Along with improvements in surgical and interventional radiology techniques, in the management of toxicities and in palliative care, the median overall survival of patients with mCRC can now be prolonged for >30 months. However, an unmet need for new treatments and biomarkers remains.

Following the publication of data from the MOSAIC study in 2004, which demonstrated the efficacy of oxaliplatin-based adjuvant chemotherapy in patients with stage III colon cancer, no major treatment advances have been made in the adjuvant setting. Moreover, only 20% of patients with resected stage III colon cancer, and only 5–10% with high-risk stage II disease really benefit from adjuvant treatment, meaning that the majority of patients are exposed to unnecessary toxicities, mostly owing to cumulative and potentially long-lasting oxaliplatin-related neurotoxicities.

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration was designed to determine whether the duration of oxaliplatin-based adjuvant chemotherapy can be decreased from 6 months, the current global standard of care, to 3 months without compromising efficacy, while also improving both tolerability and costs. In this collaboration, investigators performed a prospective, pre-planned pooled analysis of data from six randomized phase III trials designed to assess the non-inferiority of 3 months of

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Competing interests statement

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adjuvant chemotherapy with either 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (XELOX) compared with 6 months of either regimen in patients with stage III colon cancer. The results were presented at the ASCO Annual Meeting 2017 (REF. 1). This huge endeavour assembled data from nearly 13,000 patients enrolled between 2007 and 2015 in studies in 12 countries: TOSCA (Italy, the first trial to start enrolling patients in 2007), SCOT (UK, Denmark, Spain, Australia, Sweden, New Zealand), Alliance/SWOG 80702 (USA, Canada), IDEA (France), ACHIEVE (Japan), and HORG (Greece). In order to determine non-inferiority, the predefined two-sided 95% CI for disease-free survival (DFS), which was the primary end point of the study, needed to be <1.12. Overall, 3-year DFS was 74.6% in the 3-month arm and 75.5% in the 6-month arm (HR 1.07, 95% CI 1.00–1.15). Thus, from a purely statistical point of view, non-inferiority was not established, suggesting that 3 months of treatment are not as beneficial as 6 months. However, the DFS curves overlap and the absolute gain in efficacy with 6 months of treatment is <1%, while the risk of severe (grade ≥3) neurotoxicities was much higher in the 6-month arm versus the 3-month arm (16% versus 3% with FOLFOX, 9% versus 3% with XELOX; P <0.0001 for both comparisons). In addition, in the pre-planned subgroup analysis, non-inferiority was established in patients who received XELOX (HR 0.95, 95% CI 0.85–1.06), but not in those treated with FOLFOX (HR 1.16, 95% CI 1.06–1.26), and in patients with T1–3N1 disease (HR 1.01, 95% CI 0.90–1.12), but not in those with T4 or N2 disease (HR 1.12, 95% CI 1.03–1.23). On the basis of these data, the IDEA trial is leading to a paradigm shift in the adjuvant treatment of patients with stage III colon cancer. These results have created several controversies and have several shortcomings; although, despite the fact that the trial failed its primary end point, the differences in DFS are so limited, and the differences in toxicity so much better, that 3 months of oxaliplatin-based chemotherapy should be considered the standard of care for patients with T1–3 N1 stage III colon cancer. However, in patients with a higher risk of disease relapse (those with T4 or N2 disease), oncologists should continue to plan 6 months of adjuvant chemotherapy.

In the past few years, the introduction of immune-checkpoint inhibitors has dramatically improved the standard of care for many types of cancer. Nevertheless, CRC was originally shown to be resistant to this therapy in various studies. In the past 2 years, the presence of DNA mismatch repair deficiency (dMMR) has been proved to strongly predict sensitivity to immune-checkpoint inhibition in a variety of solid tumours, including mCRC[2,3]. This finding has led to the accelerated approval of pembrolizumab, an anti-PD-1 antibody, for the treatment of patients with unresectable or metastatic microsatellite-instability-high (MSI-H)/dMMR solid tumours in May 2017. This is the first example of FDA approval of an anti-cancer treatment based on the presence of a biomarker, rather than on the body location from which the tumour originated. Moving from these data, CheckMate 142, an open-label, multicentre, phase II clinical trial, was designed to assess the efficacy of nivolumab, an anti-PD-1 antibody, or nivolumab plus ipilimumab, an anti-CTLA-4 antibody, in patients with MSI-H or non-MSI-H mCRC. Results obtained using nivolumab monotherapy in patients with MSI-H mCRC in CheckMate 142 were reported in 2017 (REF. 4). A total of 74 patients with MSI-H/dMMR mCRC received nivolumab (3 mg/kg every 2 weeks) until disease progression, death, unacceptable adverse effects, or withdrawal from the study. The overall investigator-assessed objective response rate (ORR) was 31.1% at a median follow-up

duration of 12 months, while 69% of patients had disease control for ≥12 weeks. Remarkably, eight (out of 23) responders had responses lasting ≥12 months, which is even more impressive considering that 54% of patients enrolled had received at least three previous treatments. On the basis of these results, on the 31st of July 2017, the FDA granted accelerated approval to nivolumab for the treatment of patients aged ≥12 years with MSI-H/dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

These data are astonishing, although only a few patients with mCRC will benefit from these treatments. In fact, only 5% of all patients with mCRC have MSI-H/dMMR disease, meaning that almost 95% of patients are considered resistant to immune-checkpoint inhibition. For this reason, both new agents and new biomarkers are urgently needed to improve the overall survival outcomes in the majority of patients.

Beyond MSI-H/dMMR status, evidence continues to mount that tumour sidedness (right versus left) is a promising prognostic and predictive biomarker in patients with mCRC. In fact, data from studies involving tumours arising from different sides of the colon have revealed variations in molecular characteristics and clinical outcomes, which might reflect different embryological origins. Arnold *et al.*[5] investigated the prognostic and predictive relevance of the side of the primary tumour in 2,159 patients with unresectable *RAS*-wild-type mCRC enrolled in six randomized trials (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK, and 20050181) designed to compare the efficacy of chemotherapy plus anti-EGFR antibodies versus that of chemotherapy with or without bevacizumab. A significantly worse prognosis was observed in patients with right-sided tumours than in those with left-sided tumours in both the pooled experimental and control arms for overall survival (HR 2.03, 1.38, respectively; $P < 0.001$), progression-free survival (PFS; HR 1.59; $P < 0.001$, and HR 1.25; $P = 0.008$), and ORR (OR 0.38, 0.56; $P < 0.001$). In addition, right-sided tumour location was not associated with a significant level of benefit from treatment with anti-EGFR antibodies in terms of either overall survival (HR 1.12; $P = 0.38$) or PFS (HR 1.12; $P = 0.37$) compared with a significant benefit from anti-EGFR antibodies, which was observed in patients with left-sided tumours in terms of both overall survival (HR 0.75; $P < 0.001$) and PFS (HR 0.78; $P < 0.001$). Owing to the retrospective nature of this analysis, these data should be interpreted with caution. However, these findings are consistent with those of two other studies published in the same period[6,7], thus increasing the external validity of these data.

Tumour sidedness seems to be a surrogate for genetic differences that drive the development and progression of colon cancers arising in different locations. In 2015, a new consensus molecular subtypes (CMS) classification divided CRC into four distinct subgroups: microsatellite-instability immune (CMS1), canonical (CMS2), metabolic (CMS3), and mesenchymal (CMS4) — each characterized by specific pathway enrichment traits[8]. In 2017, in a retrospective analysis of data from 581 patients with *RAS*-wild-type disease enrolled in the CALGB/SWOG 80405 trial, researchers confirmed the prognostic value of the CMS classification. In addition, they were able to demonstrate that patients with CMS1 colon cancer, which is more frequently diagnosed in the right side of the colon, benefit more from bevacizumab-based treatment than from cetuximab-based treatment (median overall

survival 22.5 months versus 11.7 months; $P = 0.029$); CMS2, which is more common in patients with left-sided CRCs, is associated with the opposite sensitivity profile[9]. Further prospective analyses are warranted to validate this potentially practice-changing biomarker. However, these data are consistent across various studies, providing a sound rationale for the implementation of anti-EGFR antibodies in patients with left-sided *RAS*-wild-type mCRC, whereas bevacizumab should be preferred for those with right-sided *RAS*-wild-type mCRC.

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Key advances

- On the basis of results of the IDEA trial, 3 months, compared with the current standard-of-care 6 months, of adjuvant chemotherapy for patients with stage III colon cancer dramatically decreases the risk of neurotoxicities without compromising overall efficacy[1]
- Immune-checkpoint inhibitors targeting PD-1 (pembrolizumab and nivolumab) were approved in 2017 by the FDA for microsatellite instability-high DNA mismatch repair deficient metastatic colorectal cancer, thus providing further treatment options for these patients[2,4]
- Tumour sidedness is an emerging and promising biomarker with both prognostic and predictive value that can influence the choice of biologic agent (anti-VEGF versus anti-EGFR antibodies) for first-line treatment of patients with *RAS*-wild-type metastatic colorectal cancer[5–7]