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SYSTEMIC THERAPIES IN COLORECTAL CANCER (SM KAZMI, SECTION EDITOR)

Duration of Adjuvant Chemotherapy in Colon Cancer: Current Standards and New Updates

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Abstract

Purpose of Review Adjuvant therapy for 6 months is the standard of care for stage III colon cancer. The use of oxaliplatin-based therapy over fluoropyrimidine alone increases toxicity, including dose-dependent peripheral neuropathy. Evaluation of a shorter duration of adjuvant therapy was therefore warranted, aiming to reduce toxicity while maintaining clinical efficacy.

Recent Findings The International Duration Evaluation of Adjuvant chemotherapy (IDEA) collaboration was a pivotal prospective pooled analysis of 6 randomized phase III trials across 12 countries. IDEA evaluated the non-inferiority of 3 versus 6 months of adjuvant oxaliplatin-based chemotherapy. The 3-year disease-free survival was very similar between the 3-month and 6-month study arms. Despite this, non-inferiority was not confirmed. However, important differences were observed between FOLFOX and CAPOX regimens, and risk groups within stage III disease, which allow for greater individualization of adjuvant therapy.

Summary The IDEA results suggest 3 months of therapy is reasonable in most patients with stage III disease, especially those with low-risk disease. Importantly, 3 months of therapy is associated with a dramatic reduction in peripheral neuropathy. A thorough discussion of the risks and benefits with patients regarding the duration of therapy is required. In this review, we discuss the IDEA findings and the optimal duration of adjuvant chemotherapy in stage III colon cancer.

Keywords Colon cancer · Adjuvant chemotherapy · Duration · FOLFOX · CAPOX · Personalized

Introduction

Colon cancer is the fourth commonest cancer in the United States (US). It is estimated that it will account for 101,420 diagnoses, and colon and rectal cancer combined will be responsible for 51,020 deaths in 2019 [1]. Worldwide, colorectal cancer is the third most commonly diagnosed cancer, accounting for almost 1.81 million new cases and 862,000 deaths in 2018 [2].

The benefit of adjuvant therapy in colon cancer is well established with an approximate 30% reduction in the relative risk of tumor recurrence or death from colon cancer with fluoropyrimidine-based chemotherapy for 6 months versus surgery alone [3–5]. This benefit is largely restricted to patients with stage III disease. Findings from the landmark MOSAIC (Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer) study represented further progress, whereby the risk of death was reduced by 20% further with the addition of oxaliplatin to 5-fluorouracil (5-FU)/leucovorin (LV) alone [6, 7]. This study demonstrated an improvement in 3-year disease-free survival (DFS) in patients treated with FOLFOX (5-FU/LV/oxaliplatin) versus bolus 5-FU (3-year DFS 78% vs 73%, HR 0.77, $p = 0.002$). At longer follow-up, 5-year DFS and 6-year overall survival (OS) were improved and at nearly 10 years of follow-up there remained a significant improvement in OS in patients with stage III disease (OS 67% vs 59%, HR 0.80, $p = 0.016$) for FOLFOX over 5-FU/LV alone [8]. There was no significant difference in OS seen in stage II patients with the addition of oxaliplatin to 5-FU/LV.

The benefit of adding oxaliplatin was further confirmed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 and NO16968 studies. NSABP C-07 compared weekly bolus 5-FU/LV to FLOX (weekly 5-FU plus oxaliplatin) in stages II and III patients [9]. After 8 years of

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follow-up, there was a significant improvement in 5-year DFS in patients treated with FLOX vs 5-FU (69% versus 64%, HR 0.82, $p < 0.01$). NO16968 compared CAPOX to bolus 5-FU in patients with stage III disease. Long-term follow-up showed a 7-year DFS benefit of 63% versus 56% for CAPOX versus 5-FU (HR 0.80, $p < 0.01$) [10]. Seven-year OS was improved from 67 to 73% (HR 0.83, $p = 0.04$). Combined, these studies enrolled over 6500 patients and based on their findings 6 months of FOLFOX or CAPOX became standard of care in stage III colon cancer.

However, the benefits associated with fluoropyrimidine/oxaliplatin come with an associated cost. Oxaliplatin is associated with cumulative dose-dependent neurotoxicity which may be debilitating for many patients. Symptoms can persist for many months or years after discontinuation of treatment and can sometimes be permanent with a resultant negative impact on the quality of life. Dose reductions and early discontinuation of treatment due to neuropathy are common. While the standard of care has been to administer 12 cycles of FOLFOX (oxaliplatin dosed at 85 mg/m^2) over 6 months, NSABP-C07 indicated a similar improvement in DFS with only 9 cycles of oxaliplatin at the same dose [9], suggesting early discontinuation due to neuropathy is reasonable.

The risk and severity of neuropathy are related to the cumulative dose administered. This is particularly important in the context of adjuvant therapy where many patients will not experience disease recurrence. Therefore, oxaliplatin-induced neuropathy is a clinically relevant concern for both patients and oncologists alike. Long-term follow-up from the MOSAIC study reported that at 48 months of follow-up 15% of patients had residual neuropathy (12%, 2.8%, and 0.7% had grade 1, 2, and 3 neuropathy respectively) [7]. The incidence of chronic neuropathy was also evaluated in patients who received adjuvant FOLFOX on the N08CB (North Central Cancer Treatment Group) study [11]. Eighteen months following completion of adjuvant oxaliplatin-based therapy, 19% reported severe neuropathy as measured by the EORTC-CIPN (European Organization for Research and Treatment of Cancer Quality of Life questionnaire for patients with chemotherapy-induced peripheral neuropathy). In addition to neuropathy and other toxicities, 6 months of adjuvant oxaliplatin-based therapy is associated with significant health care resource utilization.

Duration of Adjuvant Therapy

In the 1980s, adjuvant therapy in colon cancer was administered over an 18-month period [12]. Subsequent studies found a benefit for 12 months of adjuvant therapy [13–15] before 6 months of 5-FU/LV was found to be equivalent to 12 months of 5-FU/LV plus levamisole [3, 15]. More recently, a study from the UK evaluated 3 months of protracted infusion of 5-FU versus 6 months of standard bolus 5-FU/LV and found no OS difference between the two arms. A trend toward improved relapse-free survival (RFS) and OS was reported for protracted infusion 5-FU, which was also associated with less toxicity versus 5-FU/LV [16]. Findings from this study suggested that shorter durations of adjuvant therapy should be evaluated further.

IDEA Collaboration

It is now 15 years since FOLFOX became a standard adjuvant therapy for colon cancer. While expectations were high that more progress would be made in treating patients with stages II and III colon cancer, trials evaluating irinotecan, bevacizumab, and cetuximab did not demonstrate superiority to 5-FU/LV alone or FOLFOX respectively [17–22]. The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration represents the first trial to suggest a change in standard adjuvant therapy since 2004. The overall aim of this study was to attempt to further reduce the burden of adjuvant therapy on patients with colorectal cancer without significantly compromising the rate of cure.

IDEA was an academic collaboration of clinicians and statisticians which prospectively pooled data from six randomized phase III trials across 12 countries [23]. Individual studies had been designed (with a primary hypothesis that 3 months of oxaliplatin-based therapy would be non-inferior to 6 months of therapy) to assess if reducing the exposure to oxaliplatin by 50% would result in less neuropathy without compromising the survival advantage that had previously been shown with FOLFOX. Cumulatively, these studies included 12,834 patients with stage III disease, with the understanding that a high number of patients would be needed to ensure, with confidence, that efficacy would not be sacrificed in return for decreased toxicity.

The TOSCA study was accruing patients at the time of formation of the IDEA collaboration. In this context, the different investigating groups were given autonomy to design each study appropriately for the population being studied and their preferences. This was a non-inferiority design, agreed upon by both patient advocates and oncologists. It was determined that a shorter duration of therapy should not sacrifice more than 12% of the benefit of adjuvant therapy, meaning, in statistical terms, that the upper 95% confidence interval (CI) of the hazard ratio (HR) for 3-year DFS could not exceed 1.12, the primary end-point for the study. This non-inferiority margin represented a 2.7% decrease in the 3-year rate of DFS with standard therapy (from 72 to 69.3%) which was adjudicated to be clinically acceptable.

In five of six trials, FOLFOX or CAPOX (capecitabine/oxaliplatin) was selected based on physician choice and therefore was not a randomized comparison. This resulted in significant variability between regimens administered between the

studies. Overall, approximately 60% of patients received FOLFOX and 40% were treated with CAPOX. Table 1 outlines the percentage use of CAPOX across each of the six studies. The CALGB/SWOG 80702 study evaluated only FOLFOX. SCOT and TOSCA included patients with stage II/III disease while SCOT included patients with both rectal and colon cancer. The included rectal cancer patients did not receive preoperative chemotherapy, but patients who had received short course radiation were eligible to be included. Patients with stage II disease were not included in the pooled analysis.

IDEA Results

Despite observing numerically very similar 3-year DFS rates between study arms, the criteria for non-inferiority were not met in the overall analysis. At a median follow-up of 41.8 months, the DFS HR was 1.07 (95% CI 1.00 to 1.15) with a 3-year DFS of 74.6% in the 3-month arm and 75.5% in the 6-month arm, equating to a 3-year DFS difference of 0.9%.

Results were stratified by chemotherapy regimen received. Surprisingly, there was a statistically significant interaction ($p = 0.0051$) based on whether patients received FOLFOX or CAPOX. Three months of FOLFOX was inferior to 6 months of FOLFOX (HR 1.16, 95% CI 1.06–1.26). However, 3 months of CAPOX was non-inferior to 6 months (HR 0.95, 95% CI 0.85–1.06) with a gain in 3-year DFS of 1.1% (75.9% vs. 74.8%).

In an exploratory analysis, results were also stratified by TNM stage. In patients considered at low risk of recurrence (T1–3, N1; 58.7% of patients), 3 months of therapy did meet non-inferiority criteria. Three-year DFS was 83.1% and 83.3% (HR 1.01, 95% CI 0.90–1.12) for 3 months vs. 6 months of therapy respectively. In those with T4 tumors or 4 or more positive nodes (T4, N2 or both; 41.3% of patients), 6 months of therapy was superior to 3 months (HR 1.12, 95% CI 1.03–1.23) despite a difference in 3-year DFS of only 1.7% (62.7% vs 64.4%).

When risk groups were then evaluated by chemotherapy regimen received, 3 months of CAPOX was non-inferior to 6 months of therapy in low-risk T1–3, N1 patients (HR 0.85, 95% CI 0.71–1.01), 3-year DFS 85% vs 83.1% in favor of 3 months of therapy. In high-risk T4, N2 patients, study results appeared favorable. Three months of CAPOX was associated with similar 3-year DFS to 6 months (64.1% vs 64%) but did not reach criteria for non-inferiority (HR 1.02, 95% CI 0.89–1.17) because the upper 95% confidence interval of the HR for 3-year DFS exceeded 1.12. In contrast, 6 months of FOLFOX was superior to 3 months irrespective of risk group, 3-year DFS 76% versus 73.6% for 6 months versus 3 months of therapy. In patients with high-risk disease, 6 months of FOLFOX resulted in improved DFS (64.7% vs 61.5%) compared with 3 months of therapy (HR 1.20, 95% CI 1.07–1.30). Finally, in patients with T4 disease, irrespective of nodal positivity (20% of the study population), there did appear to be an advantage for 6 months of therapy. The 3-year DFS in this group was 58.1% versus 61.4% (HR 1.16 (1.03–1.31), $p = 0.01$) for 3 months versus 6 months of therapy. However, no significant difference was observed for 6 months of therapy compared with 3 months of therapy in patients with N1 versus N2 disease.

Peripheral sensory neuropathy of grade 2 or higher was significantly reduced ($p < 0.001$) during active therapy and in the month following treatment discontinuation in patients who received 3 months of therapy. In FOLFOX-treated patients, the rate of clinically relevant neuropathy (≥ 2) was 16.6% with 3 months of therapy and 47.7% with 6 months of therapy. Similarly, in patients who received CAPOX, grade ≥ 2 neuropathy occurred in 14.2% and 44.9% of patients who received 3 months and 6 months of therapy respectively. The rate of grade 3/4 neuropathy was substantially reduced in patients who received 3 months of therapy. In general, a shorter duration of therapy was associated with significantly lower rates of adverse events including diarrhea, mucositis, fatigue, hand-foot syndrome, neutropenia and thrombocytopenia.

The IDEA study also provides prognostic information for stage III low-risk and high-risk disease demonstrating an

Table 1 The IDEA collaboration of six studies across 12 countries

Trial	Countries	Regimen	Stage	Stage III patients (*n*)	Tumor location	T4 disease	% CAPOX
SCOT	UK, Denmark, Spain, Australia, Sweden, New Zealand	CAPOX or mFOLFOX6	II, III	3983	Colon/rectum	29%	67%
TOSCA	Italy	CAPOX or mFOLFOX4	II, III	2402	Colon	12%	36%
Alliance/SWOG 80702	US, Canada	mFOLFOX6	III	2440	Colon	15%	0%
IDEA-France	France	CAPOX or mFOLFOX6	III	2010	Colon	18%	10%
ACHIEVE	Japan	CAPOX or mFOLFOX6	III	1291	Colon	28%	75%
HORG	Greece	CAPOX or mFOLFOX4	III	708	Colon	14%	58%

approximate 20% difference in 3-year DFS (60% versus 80%) for high-risk T4 and/or N2 disease compared with low-risk T3, N1 disease. Table 1 outlines the individual trials including in the IDEA collaboration, which are also discussed in more detail below. Table 2 summarizes the above results by treatment regimen and risk groups.

SCOT

The SCOT trial enrolled the largest number of patients, 6088, both with high-risk stage II and stage III disease and included patients with both colon and rectal cancer, the only IDEA study to do so [24]. Patients were randomized to 3 or 6 months of physician's choice CAPOX or FOLFOX6. Two-thirds of patients received CAPOX. At a median follow-up of 37 months, there was only a 0.4% difference in 3-year DFS (76.7% vs 77.1%) with a HR of 1.006 (95% CI 0.909–1.11) proving non-inferiority as the upper limit of the CI was less than the prespecified non-inferiority margin of 1.13. In keeping with the overall IDEA analysis, subgroup analyses demonstrated that for low-risk stage III patients and those treated with CAPOX, 3 months of therapy was non-inferior. However, in high-risk stage III patients and those who received FOLFOX, non-inferiority of 3 months of therapy was not demonstrated. In a post-hoc analysis, the impact of tumor sidedness on DFS and the 3- versus 6-month comparison was evaluated [25]. Patients with right-sided tumors had a significantly worse 3-year DFS (73% versus 80%, HR 1.401, 95% CI 1.216–1.615; $p < 0.0001$). After adjusting for T and N-stage, there remained a significant difference in DFS. However, the data did not suggest that sidedness affected the impact of chemotherapy duration on DFS.

TOSCA

Like SCOT, the TOSCA study randomized patients with stage II or III colon cancer to 3 or 6 months of physician's choice CAPOX or FOLFOX4 [26]. CAPOX was chosen in 36% of patients. At a median follow-up of 62 months, the difference in RFS was 1.9% between groups, 83% and 81.1% in the 6 months and 3 months arms respectively. In stage III patients, the RFS HR for 3 months versus 6 months of therapy was 1.07 (95% CI 0.91–1.26). Non-inferiority was not met as the prespecified upper boundary of the HR for RFS had to be less than 1.20 for results to be declared non-inferior. Non-inferiority was also not demonstrated in either chemotherapy subgroup. However, while the RFS curves for 3 months versus 6 months of CAPOX were superimposed with a HR of 0.98 (95% CI 0.77–1.26), the 3-year RFS difference with FOLFOX was 3.2% and 5% at 3 and 5 years respectively, in favor of 6 months of FOLFOX (HR 1.22; 95% CI 1.02–1.44).

IDEA-France

This study enrolled 2010 patients with stage III disease to physician's choice CAPOX or mFOLFOX6 (90% received mFOLFOX6) [27]. IDEA-France was designed as part of the larger IDEA collaboration and did not have its own sample size/power calculation. Efficacy analyses were therefore descriptive. Three months of adjuvant therapy was associated with a numerically decreased 3-year DFS rate (72% vs 76%) compared with 6 months of therapy (HR 1.24, 95% CI 1.05–1.46). In subgroup analyses by risk group, 6 months of therapy compared with 3 months of therapy resulted in a 3% and 6% difference in DFS in low-risk and high-risk stage III patients respectively.

HORG

Like IDEA-France, HORG was designed as part of the overall collaboration. This study enrolled 708 stage III patients, 58% received FOLFOX [28]. At a median follow-up of 54 months, 3-year DFS was 73.2% in the 3-month arm and 74.9% in the 6-month arm. Consistent with the IDEA results, the difference

Table 2 Three-year disease-free survival (DFS) by treatment regimen and risk groups

Group	3-year DFS (%)			
	3-month	6-month	HR (95% CI)	Conclusion
Regimen and risk groups combined	74.6%	75.5%	1.07 (1.00–1.15)	Not proven
Low-risk CAPOX + FOLFOX	83.1%	83.3%	*1.01 (0.90–1.12)*	*Non-inferior*
High-risk CAPOX + FOLFOX	62.7%	64.4%	1.12 (1.03–1.23)	Inferior
Low-risk; CAPOX	85%	83.1%	*0.85 (0.71–1.01)*	*Non-inferior*
Low-risk; FOLFOX	81.9%	83.5%	1.10 (0.96–1.26)	Not proven
High-risk; CAPOX	64.1%	64%	1.02 (0.89–1.17)	Not proven
High-risk; FOLFOX	61.5%	64.7%	1.20 (1.07–1.35)	Inferior

CI, confidence interval; values in italics depict non-inferiority

in 3-year DFS in patients treated with CAPOX was small (74.7% vs 74.8%), contrasting with the FOLFOX-treated patients where 3-year DFS was 71.8% vs 77.7%.

ACHIEVE

ACHIEVE enrolled 1291 Japanese patients with stage III disease [29]. Most patients received CAPOX. In both the overall population and subgroup analyses, the results were consistent with the results of the overall IDEA results. Numerically, the DFS was higher in the 3-month arm (79.5% vs 77.9%; HR 0.95, 95% CI 0.758–1.201). Again, CAPOX appeared superior to FOLFOX and in patients treated with 3 months of therapy patients with low-risk disease had a more favorable HR than those with high-risk disease.

CALGB/SWOG 80702

The CALGB/SWOG 80702 study was conducted in North America and was the only study to use only FOLFOX. The results have not been presented or published separately to the larger collaborative results.

Interpreting the Results

The divergent results reported for FOLFOX and CAPOX in the overall IDEA collaboration was a surprising finding. Previous studies, especially in the metastatic setting, have suggested that the efficacy of both fluoropyrimidines (5-fluorouracil and capecitabine) is similar [30]. In the adjuvant setting, bolus 5-FU is comparable with capecitabine [31]; however, the equivalence of infusional 5-FU to capecitabine has not been shown. The contradictory outcomes described in the TOSCA, SCOT, IDEA-France, and ACHIEVE studies may also be explained by the differences in FOLFOX and CAPOX usage between the studies. Other potential explanations for the difference include heterogeneity in dose intensity or baseline characteristics between studies. However, IDEA-France achieved the best dose intensity for 3 months of therapy, followed by TOSCA, yet neither of these studies met non-inferiority, while the SCOT trial did. Similarly, SCOT and IDEA-France had a similar distribution of performance status 0/1 patients, yet their results are most divergent. Ultimately, the difference in outcomes between these studies may be explained by the percent use of FOLFOX or CAPOX between the studies. The overall DFS results in the SCOT and ACHIEVE studies, where 67% and 75% of patients respectively received CAPOX, suggest that 3 months of therapy was comparable to 6 months of therapy. In contrast, the TOSCA and IDEA-France studies, where 64% and 90% of patients respectively received FOLFOX, did not meet non-inferiority criteria for 3 months versus 6 months of therapy.

One explanation that has been proposed is the difference in early dose intensity between the regimens. During the first 4 weeks of CAPOX therapy, patients receive 260 mg/m^2 of oxaliplatin. In contrast, patients treated with FOLFOX receive 170 mg/m^2 of oxaliplatin. While the cumulative dose at the end of 3 months of therapy is almost identical between the regimens, it is possible that the first weeks of treatment are most crucial in delivering the benefit of adjuvant therapy. Another potential explanation is that continuous fluoropyrimidine exposure with capecitabine is superior to twice monthly infusional fluorouracil. Two previous studies support this hypothesis. Firstly, the X-ACT (Xeloda in Adjuvant Colon Cancer Therapy) trial compared 6 months of adjuvant capecitabine to bolus 5-FU/LV in patients with resected stage III colon cancer [31]. There was a trend toward superior DFS with capecitabine compared with 5-FU/LV (p = 0.05). Another trial, mentioned above, evaluated 6 months of bolus 5-FU/LV versus 12 weeks of protracted infusion of 5-FU in patients with stages II and III colorectal cancer [16]. There was a suggestion of better outcomes in patients who received continuous infusional 5-FU, despite a shorter duration of therapy received.

An important caveat is that randomization was not stratified by choice of regimen (FOLFOX or CAPOX) and the subgroup analysis of CAPOX versus FOLFOX was not preplanned. Therefore, there may have been patient factors (e.g., renal function, compliance) that biased the physician's choice of FOLFOX or CAPOX given that capecitabine is considered more toxic than 5-FU with a higher dose of oxaliplatin given at each dose due to cycle duration. Thus, definitive conclusions cannot be drawn regarding the choice of therapy. However, taken together, the data do suggest that CAPOX is the more optimal adjuvant regimen for colon cancer. While this finding has not been observed in the treatment of metastatic disease [30], metastatic disease may behave differently to micrometastatic occult disease, as evidenced by the failure of adjuvant irinotecan, cetuximab, and bevacizumab trials. Furthermore, the sheer size of the sample assessed in this analysis undercuts most of these criticisms.

Another interesting question raised by the IDEA trials is the optimal duration of therapy in patients with stage II disease, who were included in the SCOT and TOSCA studies. In the SCOT study, subgroup analysis reported a HR of 0.988 (95% CI 0.746–1.31) for 3 months versus 6 months therapy duration in patients with high-risk stage II disease. However, somewhat counter-intuitively, the TOSCA study found that 3 months of chemotherapy was inferior to 6 months of therapy (HR 1.41, 95% CI 1.05–1.89; p = 0.022). The absolute RFS differences between the arms were 5.6% and 5.9% at 3 and 5 years in favor of 6 months of treatment. However, the interaction test for stage was not significant (p = 0.108). TOSCA is

also undertaking translational studies, including MMR status, an important prognostic factor in stage II patients [32] which may help further in the interpretation of this data. In the context of a negative interaction test, low number of events observed in TOSCA stage II patients, and the SCOT results, it is possible that these results are the consequence of chance. However, it is also possible that stage II disease is biologically different from stage III disease [33]. The results could also be impacted by patients with stage II T4 disease for which there may be a greater benefit for a longer duration of adjuvant therapy. The IDEA 2 collaboration is also undertaking a pooled analysis of stage II patients to further evaluate this question. For now, the standard of fluoropyrimidine monotherapy for 6 months in patients with microsatellite stable stage II colon cancer remains unchanged.

Putting the IDEA Results Into Practice

The National Comprehensive Cancer Network (NCCN) has incorporated the IDEA data into guidelines, representing the first important change to the adjuvant therapy guidelines since 2004. For low-risk T1–3, N1 disease, the preferred regimen is CAPOX for 3 months (category 1) or FOLFOX for 3–6 months (category 1 for 6 months only). In patients with high-risk stage III T4, N1 or any T, N2 disease, the preferred option is CAPOX for 3–6 months (category 1 recommendation for 6 months duration) or alternatively FOLFOX for 6 months.

The results of the individual IDEA studies and the overall collaboration have been extensively deliberated. Overall, IDEA has provided helpful information to oncologists treating colon cancer, providing a framework for discussion with patients regarding the clinical value of 6 months versus 3 months of therapy. It allows for better identification of patients at higher risk of recurrence and individualization of the duration of adjuvant therapy based on the goals of care, patient preference in terms of the degree of toxicity they consider acceptable, and their tolerance of treatment. The dramatic reduction in neurotoxicity is clinically meaningful. The risk-benefit analysis overall appears to favor 3 months of therapy, especially when CAPOX is used, and especially in patients considered at lower risk of recurrence or those who are concerned about the risk of persistent neuropathy.

In the US, FOLFOX has generally been favored over CAPOX. Capecitabine is less well tolerated in the US than in other geographic regions. A higher incidence of hand-foot syndrome and diarrhea has been reported in American patients treated with fluoropyrimidines than in Asian patients [34], and there has been a reluctance to prescribe CAPOX for this reason which may have implications for the degree of shift in practice to CAPOX over FOLFOX in the US. The CALGB/SWOG 80702 study which enrolled North American patients did not evaluate CAPOX. Again, given that the use of FOLFOX or CAPOX was not randomized across the IDEA studies, 6 months of FOLFOX may remain standard in the US for high-risk patients, although the duration of therapy warrants individualized discussion given the magnitude of benefit, and a clear increase in toxicity, with 6 months of treatment. Ultimately, this data allows for early discontinuation of treatment when excessive toxicity occurs. In patients receiving 6 months of therapy, the emergence of neuropathy should be closely monitored, with discontinuation of treatment when this occurs, to avoid precipitating worsening cumulative neuropathy which may be may long lasting.

Further analysis of the IDEA dataset may lead to greater clarity regarding the optimal duration of therapy. Molecular analysis of the SCOT (TransSCOT) and TOSCA studies is planned, aiming to explore other predictors of outcome. RAS, BRAF, microsatellite instability (MSI), primary tumor location, and immune and inflammatory profiles (immunoscore) may better delineate the most important factors that impact on outcome. It is likely that only a small proportion of stage III patients would be cured with 6 months of therapy but not three. Identifying these patients would advance our treatments and allow us to reduce toxicity further.

Conclusion

The IDEA collaboration highlights the critical importance of publicly funded studies which allow key questions to be evaluated. This was a global study whose results are clinically meaningful, allowing us to individualize treatment duration, realizing that 3 months of therapy may be sufficient for most patients with stage III colon cancer. Going forward, questions remain regarding future trial design and whether flexible backbone/treatment duration should be allowed. For rectal cancer, the total duration of peri-operative therapy remains 6 months. Total neoadjuvant therapy (TNT) is also a standard in rectal cancer [35], and the IDEA results raise questions about the optimal duration of TNT. A study evaluating adjuvant chemotherapy plus immunotherapy (NCT02912559) is ongoing in MSI high stage III colon cancer—the results of IDEA may also have implications for the appropriate duration of adjuvant therapy in this setting.

The IDEA collaboration is an important step forward in the adjuvant treatment of colon cancer. Despite this, decision-making regarding adjuvant therapy remains complex, especially as we remain unable to identify those patients with micrometastatic disease and whether or not this disease will respond to adjuvant therapy. The risk of recurrence, the magnitude of risk reduction with adjuvant therapy, and risk of toxicity should be assessed in each patient to guide treatment decisions.

Compliance With Ethical Standards

Conflict of Interest Megan Greally declares no potential conflicts of interest.

David H. Ilson serves on the advisory board of Taiho, Pieris, Roche, Astra Zeneca, Bayer, Bristol-Myers Squibb, Merck, and Astellas.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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