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Do we have a clear IDEA for the duration of chemotherapy in stage III colorectal cancer?

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Introduction

Colorectal cancer (CRC) is a health problem rating third in incidence and fourth in mortality [1]. This discrepancy between incidence and mortality is attributed to the earlier diagnosis and the effectiveness of treatments in the early stages of CRC [2]. Stage III is very heterogeneous with different prognostic subgroups that may be even better than some stage II subgroups and commonly overtreated and exposed to toxicities [3]. Over the years, the tolerability and efficacy was improved with different 5 -FU administration schemes [4]. On the other hand, oxaliplatin-based sensory neurotoxicity depends on the cumulatively administered dose of the drug. This toxicity can be severe and persist long beyond the actual treatment and affects activities of daily living [5]. This paper details the perks and limitations of the available data that evaluates the efficacy of adjuvant shorter chemotherapy regimen comparing three and six-month treatments in CRC.

Overview of the available trials comparing three versus six months of adjuvant chemotherapy

To date, six major phase III randomized control trials have been conducted to compare three versus six cycles of adjuvant chemotherapy in stage III CRC (Tables 1 and 2). These trials were conducted concurrently in six worldwide regions including ACHIEVE (Japan), HORG (Greece), ALLIANCE/SWOG (United States, Canada), IDEA FRANCE (France), TOSCA (Italy) and SCOT (United Kingdom, Australia, New Zealand, Spain, Denmark and Sweden) [6–9]. The patients characteristics in these trials were similar for age (61-67 years), gender distribution (males 50.3-59.2%), ECOG performance status 0-1, and number of lymph nodes dissected (18-20 lymph node, except for the SCOT trial where this number was not reported). Median follow-up varied between the trials and ranged between 34.9 and 61.7 months. The efficacy outcomes differed between due to patients' heterogeneity, inclusion of stage II colon cancer and different regimen preferences among physicians. Some of these trials confirmed the non-inferiority of the 3-month regimen while others failed [6–9]. These trials reported a significant decrease in grade 3/4 oxaliplatin-related toxicity between three and six months of chemotherapy [6–9].

Pooled analysis of the available trials comparing three versus six months of adjuvant chemotherapy

The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) study is a pooled analysis of the six trials at patient-data level to evaluate the noninferiority of adjuvant therapy with either Folfox (fluorouracil, leucovorin, and oxaliplatin) or Capox (capecitabine and oxaliplatin). The individual data from the Alliance/SWOG and the HORG studies were not included due to the absence of mature data. This report included only the findings with respect to patients with stage III CRC. The primary endpoint of this study was 3-year DFS. Subgroup analysis of non-inferiority within each regimen (Folfox vs Capox and three vs six months) and risk

Table 1: Data published in the ESMO 2017 on the available individual regional data within the IDEA study

Trial Name	N in mITT (pp)										
SCOT	6088	**Regimen**	**XELOX**		HR	**FOLFOX**		HR	**Combined**		HR
		Duration	3 mo.	6 mo.		3 mo.	6 mo.		3 mo.	6 mo.	
		Low Risk	NA	NA	NA	NA	NA	NA	85.3	84	0,907 (0,749-1,097)
		High Risk	NA	NA	NA	NA	NA	NA	63	64.8	1,065 (0,932-1,218)
		All Risk	76.9	76.1	0,944 (0,835-1,067)	76.3	79.2	1,156 (0,962-1,388)			
Comments : 18,1% rectal cancer / 18,3% stage II / 67,5% received XELOX											
IDEA France	2022 (1757)	**Regimen**	**XELOX**		HR	**FOLFOX**		HR	**Combined**		HR
		Duration	3 mo.	6 mo.		3 mo.	6 mo.		3 mo.	6 mo.	
		Low Risk	NA	NA	NA	81	83	1,15 (0,89-1,49)	80	83	1,15 (0,91-1,47)
		High Risk	NA	NA	NA	58	66	1,44 (1,14-1,82)	59	65	1,38 (1,1-1,73)
		All Risk	72	71	0,97 (0,59-1,59)	72	76	1,24 (1,05-1,46)			
Comments : 10% Xelox /Xelox data not sufficient											
ACHIEVE	1313 (1291)	**Regimen**	**XELOX**		HR	**FOLFOX**		HR	**Combined**		HR
		Duration	3 mo.	6 mo.		3 mo.	6 mo.		3 mo.	6 mo.	
		Low Risk	92.6	87.9	0,64 (0,38-1,08)	83.9	85.1	1,24 (0,59-2,6)	90.5	87.3	0,81 (0,53-1,24)
		High Risk	66.6	69	1,06 (0,76-1,48)	62.3	60	1,09 (0,67-1,78)	65.4	66.5	1,07 (0,81-1,40)
		All Risk	81.4	79.7	0,9 (0,68-1,2)	73.9	72.3	1,07 (0,71-1,6)			
Comments: 75% Xelox											
TOSCA	3715 (3614)	**Regimen**	**XELOX**		HR	**FOLFOX**		HR	**Combined**		HR
		Duration	3 mo.	6 mo.		3 mo.	6 mo.		3 mo.	6 mo.	
		Low Risk	NA	NA	NA	NA	NA	NA	NA	NA	
		High Risk	NA	NA	NA	NA	NA	NA	NA	NA	
		All Risk	82.5	82.5	0,98 (0,77-1,26)	80.4	83.3	1,23 (1,03-1,46)			
Comments: 34% Xelox/ 34,7% stage II/ Interaction p value: 0.140											
IDEA	12843	**Regimen**	**XELOX**		HR	**FOLFOX**		HR	**Combined**		HR
		Duration	3 mo.	6 mo.		3 mo.	6 mo.		3 mo.	6 mo.	
		Low Risk	85	83.1	0,85 (0,71-1,01)	81.9	83.5	1,1 (0,96-1,26)	83.1	83.3	1,01 (0,9-1,12)
		High Risk	64.1	64	1,02 (0,89-1,17)	61.5	64.7	1,2 (1,07-1,35)	62.7	64.4	1,12 (1,03-1,23)
		All Risk	75.9	74.8	0,95 (0,85-1,06)	73.6	76	1,16 (1,06-1,26)			

subgroups (low risk for T1-3 N1 tumors and high risk for T4 or N2 tumors) was assessed. The statistical significance of the

Table 2. Overall comparison of 3-y DFS between 3 and 6 months of adjuvant chemotherapy

Study	3-month DFS	6-month DFS	HR (95% CI)	p value
SCOT	76,7 (75,1-78,2)	77,1 (75,6-78,7)	1,006 (0,909-1,114)	0.012
IDEA France	72 (69-75)	78 (75-80)	1,36 (1,14-1,63)	0.0007
TOSCA	81.1	83	1,14 (0,99-1,32)	0.506
ACHIEVE	79,5 (76,2-82,4)	77,9 (74,4-80,9)	0,95 (0,76-1,2)	NA
IDEA	74.6	75.5	1,07 (1-1,15)	NA

DFS: Disease free survival; HR: hazard ratio; NA: not available

non-inferiority between two subgroups was considered if the 2-sided 95% confidence interval for the DFS hazard ratio (HR) were to be below 1.12 to avoid a sacrifice of more than 12% of the benefits generated by the administration of adjuvant therapy. This margin was chosen on the basis of clinical acceptability, since it corresponded to a worsening of 2.7% in the 3-year DFS from 72 to 69.3% [10]. The statistical analysis of the IDEA trial data used the per-protocol population which is compatible with a non-inferiority study. Patients who received less than three months of therapy were excluded [11].

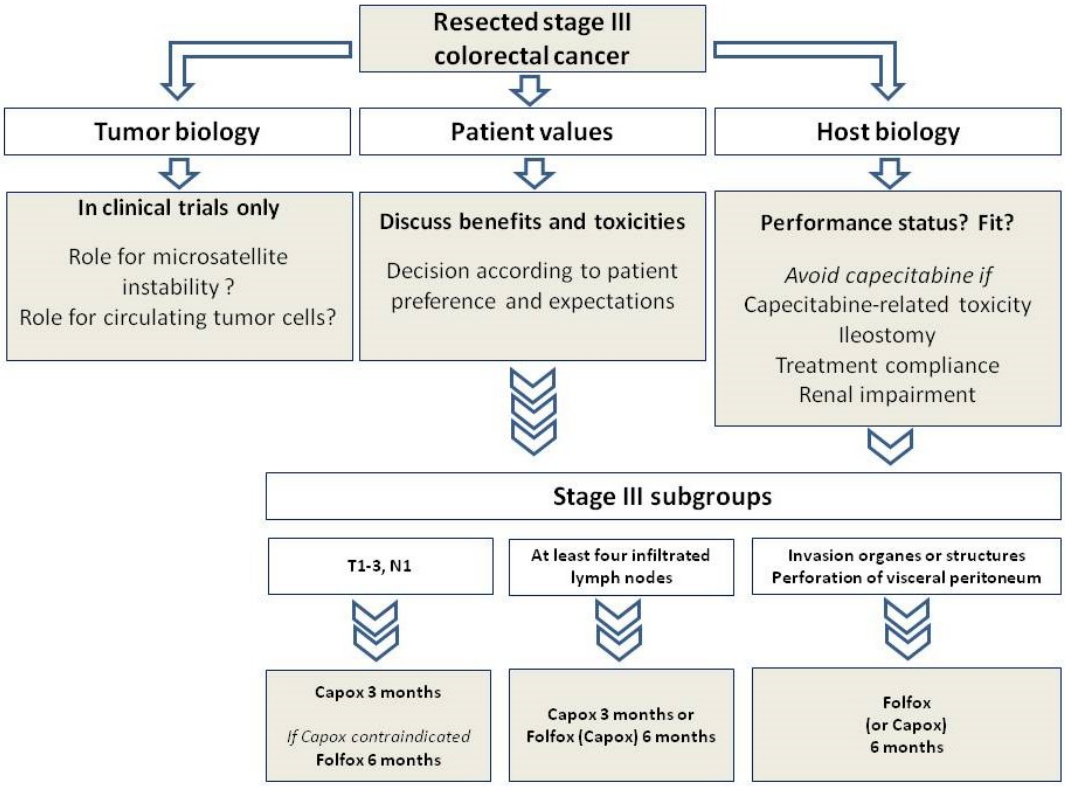
The analysis included 12,834 patients with a median follow-up of 39 months. Three months of adjuvant therapy was not "non inferior" in 3-year DFS to six month of adjuvant therapy (74.6 vs 75.5%; HR=1.07, 95% CI of 1-1.15) [11]. From a statistical standpoint, the primary endpoint of the IDEA study was not met. The dissection of the available data with the pre-planned comparisons has led to the following conclusions. Non-inferiority of three-month chemotherapy was confirmed with Capox (75.9 vs 74.8%; HR=0.95, 95%CI 0.85-1.06) but remained unproven with Folfox (73.6 vs 76.0%; HR=1.16, 95%CI 1.06-1.26). The difference between the regimens is highly significant (test for interaction p=0.006) [11]. Non-inferiority three-month chemotherapy was also confirmed in the lower risk patients (83.1 vs 83.3%; HR=1.01, 95%CI 0.90-1.12) but remained unproven in high risk (62.7 vs 64.4%; HR=1.12, 95% CI 1.03-1.23). The interaction test according to risk groups was equal to 0.11 with moderate difference between the risk subgroups [11].

The available trials did not randomize patients to three months of Capox versus six months of Folfox. The main dilemma remains that Capox for three months could not be directly compared to Folfox for six months with marginal 3-year DFS differences (76 vs 75.9%). A recent meta-analysis has confirmed similar DFS with oral and intravenous fluoropyrimidines (HR=0.92; 95%CI 0.84-1.00) [12]. The remaining difference apart from the treatment duration remains the higher doses of oxaliplatin in the first month with the Capox regimen (170 mg/sqm in Folfox versus 260 mg/sqm in Capox).

The major clinical implications can be withdrawn from the following analysis by risk group and chemotherapy regimen. Three and six months of Capox were statistically equivalent for 3-year DFS among low-risk (85.0 vs 83.1%; HR=0.85, 95%CI, 0.71-1.01) and high risk tumors (64.1 vs 64.0%; HR=1.02, 95%CI 0.89-1.17). Six months of Folfox is always superior to three months independent of risk groups with a possibility to shorter duration of treatment in the N2 subgroup of high risk patients (61.6 vs 61.8%, HR=1.07, 95%CI 0.96-1.19) [11]. These findings preclude a superiority of Capox over Folfox although high risk tumors were more prevalent in the first (24.3 vs 18.3%; p<0.0001). The continuous and prolonged exposure to 5-FU components might explain this improved efficacy in the adjuvant setting [13]. Also, three-month infusional 5-FU was not inferior to six-month bolus 5FU/leucovorin and allowed better quality of life [14]. The IDEA study showed also that the prevalence of adverse events is reduced with the shorter duration of adjuvant therapy independent of the chemotherapy regimen. Neurotoxicity of grade 2 or higher was substantially lower in the 3-month therapy group (14.2-16.2 vs 44.9-47.7%). The prevalence of other adverse events such as diarrhea, nausea, mucositis, neutropenia, thrombocytopenia, fatigue, and the hand-foot syndrome were also substantially lower with a shorter treatment duration [11].

Implications in clinical practice and future directions

The level of benefit from adjuvant therapy could affect the patient's decision in the choice of his therapy duration [15]. The IDEA study provided clear data to spare three months of unnecessary chemotherapy and increased toxicity in 60% of stage III CRC patients (figure 1). Many questions remain unanswered concerning the management of patients with poor performance status (PS≥2), geriatric patients and microsatellite instability cancer patients. Elderly cancer of 70 years and older with stage III CRC, may gain a similar survival benefit with adjuvant oxaliplatin-doublet chemotherapy (HR 0.54 95% CI 0.33 – 0.88, p=0.009) as younger patients but the optimal regimen and duration are not determined [16]. Stage II MSI CRC can be spared chemotherapy but the role of MSI in stage III CRC is still under



research. Two main studies have shown conflicting results concerning the benefit of chemotherapy in these patients [17,18].

Conclusion

To date, the IDEA study provides the strongest body of evidence that allows the individualization of treatment duration on the basis of treatment, patient preference, and disease characteristics. Physicians must keep in mind that the study design included heterogeneous populations treated within different clinical practices.

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