Preliminary tolerance analysis of adjuvant chemotherapy in older patients after resection of stage III colon adenocarcinoma from PRODIGE 34 – FFCD 1402 - ADAGE randomized phase III trial.

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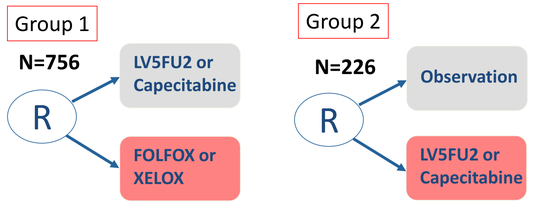
Background

Colon adenocarcinoma occurs mainly in older patients. Oxaliplatin based adjuvant chemotherapy has demonstrated an improvement on disease-free survival (DFS) after a stage III colon cancer resection in young patients. Nevertheless, the benefit of adjuvant chemotherapy is matter of debate in older patients.

Patients & Methods

The purpose of ADAGE trial is to compare the DFS obtain with oxaliplatin combined with fluoropyrimidine to fluoropyrimidine alone in fit patients over 70 years (group 1) and fluoropyrimidine to observation in frail patients (group 2) after resection of a stage III colon cancer. We here report a preliminary tolerance analysis on 50% of the first patients enrolled in the study.



Treatment: Planned for 6 months (12 cycles if LV5FU2 or FOLFOX or 8 cycles if capecitabine or XELOX), should start within 12 weeks after surgery

Mains eligibility criteria

- Age over 70 years
- Stage III colon or upper rectal adenocarcinoma
- R0 resection of the primary tumor
- Patient considered able to receive chemotherapy
- No previous chemotherapy for colon cancer
- Written informed consent
- No other cancer uncontrolled for less than 2 years
- Neutrophils >2000/mm^3 for group 1 and neutrophils >1500/mm^3 for group 2, platelets >100,000/mm^3, haemoglobin >9 g/dL

Randomization according to a 1:1 ratio.
Stratification: center, gender, stage (IIIA vs IIIB vs IIIC), occlusion and/or perforation (yes vs no) and independent activity of daily living score (IADL: normal vs abnormal).

Safety is evaluated based on laboratory and clinical tests before each cycle.

Patients and tumor characteristics

The analysis was performed on 491 patients (378 in group 1 and 113 in group 2).
The toxicity was reported in the 434 patients treated excluding the 57 patients in observation arm of group 2.

Characteristics		LV5FU2 or capecitabine	FOLFOX4 or XELOX	Total Group 1	Observation	LV5FU2 or capecitabine	Total Group 2
		N=189	N=189	N=378	N=57	N=56	N=113
Sex (n=491)	Male	111 (58.7%)	106 (56.1%)	217 (57.4%)	28 (49.1%)	28 (50.0%)	56 (49.6%)
Age	Median (extremes)	76.9 (70-90)	75.8 (70-88)	76.4 (70-90)	83.4 (71-89)	82.7 (70-91)	83.1 (70-91)
ECOG (n=462)	0	110 (60.8%)	104 (57.8%)	214 (59.3%)	12 (23.1%)	17 (34.7%)	29 (28.7%)
	1	62 (34.3%)	71 (39.4%)	133 (36.8%)	27 (51.9%)	21 (42.9%)	48 (47.5%)
	2	8 (4.4%)	5 (2.8%)	13 (3.6%)	13 (25.0%)	10 (20.4%)	23 (22.8%)
	3	1 (0.6%)	0 (0.0)	1 (0.3%)	0 (0.0)	1 (2.0%)	1 (1.0%)
Hemoglobin (gr/dl)	<10 (Women), <11 (Men)	46 (24.6%)	47 (24.9%)	93 (24.7%)	25 (43.9%)	22 (40.0%)	47 (42.0%)
Renal insufficiency	Creatinine clearance* ≤45 mL/min	7 (3.7%)	4 (2.1%)	11 (2.9%)	2 (3.6%)	2 (3.6%)	4 (3.6%)
Hypoalbuminemia	≤35 g/L	28 (16.7%)	24 (14.0%)	52 (15.3%)	14 (29.2%)	11 (21.2%)	25 (25.0%)
Stage (n=488)	Stage IIIA	19 (10.2%)	24 (12.7%)	43 (11.4%)	4 (7.0%)	4 (7.3%)	8 (7.1%)
	Stage IIIB	139 (74.3%)	134 (70.9%)	273 (72.6%)	43 (75.4%)	43 (78.2%)	86 (76.8%)
	Stage IIIC	29 (15.5%)	31 (16.4%)	60 (16.0%)	10 (17.5%)	8 (14.5%)	18 (16.1%)
Occlusion or perforation (n=487)	Yes	29 (15.5%)	34 (18.0%)	63 (16.8%)	10 (17.5%)	14 (25.5%)	24 (21.4%)
Primary localization (n=487)	Left colon	82 (43.9%)	87 (46.0%)	169 (44.9%)	20 (35.7%)	24 (43.6%)	44 (39.6%)
	Right colon	103 (55.1%)	96 (50.8%)	199 (52.9%)	34 (60.7%)	29 (52.7%)	63 (56.8%)
	Left and right colon	0 (0.0)	1 (0.5%)	1 (0.3%)	2 (3.6%)	0 (0.0)	2 (1.8%)
	Upper rectum	2 (1.1%)	5 (2.6%)	7 (1.9%)	0 (0.0)	2 (3.6%)	2 (1.8%)
Surgery in emergency (n=487)	Yes	27 (14.4%)	26 (13.8%)	53 (14.1%)	5 (8.9%)	11 (20.0%)	16 (14.4%)
MMR Status (n=154)	MSI	10 (17.5%)	9 (16.1%)	19 (16.8%)	3 (15.0%)	7 (35.0%)	10 (25.0%)

Geriatric evaluation

Mains characteristics	Group 1	Group 2
Abnormal IADL	23%	62%
No caregiver	26%	28%
Fall ≤6 months	9%	14%
Altered depression score	28%	40%
Fail of one-leg balance	20%	59%
Impaired cognition	21%	38%
G8 score <14	74%	94%
Undernutrition	35%	48%

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Treatment delivered

	Groupe 1 N=189 Fluoropyrimidine	Groupe 1 N=189 FOLFOX or XELOX	Groupe 2 N=56 Fluoropyrimidine
Treatment started	185 (97.9%)	187 (98.9)%	47 (83.9%)
Type of fluoropyrimidine	5FU: 153 (82.7%) Cape.: 31 (16.8%)	FOLFOX: 166 (88.8%) XELOX: 21 (11.2%)	5FU: 17 (36.2%) Cape.: 30 (63.8%)
Median duration of treatment	5.1 months	5.3 months	5.0 months
At least one cure delayed	104 (56.2%)	125 (66.8%)	28 (59.6%)
Early stop of treatment	33 (17.8%)	40 (21.4%)	18 (38.3%)

Observed toxicities

Toxicities grade 1-2 / 3-4	Group 1: N=189 Fluoropyrimidine,	Group 1: N=189 FOLFOX or XELOX	Group 2: N=56 Fluoropyrimidine
Neurologic	20% / 1%	87% / 21%	19% / 4%
Asthenia	59% / 4%	64% / 8%	49% / 11%
Anorexia	7.6% / 1.1%	28.3% / 2.1%	12.8% / 0%
Diarrhoea	42% / 4%	49% / 9%	40% 6%
Mucositis	24% / 1%	25% / 2%	19% / 0%
Vomiting	7% / 1%	13% / 2%	4% / 0%
Cardiac disorder	2.2% / 0%	1.6% / 1.1%	6.4% / 4.3%
Neutropenia	18% / 3%	36% / 22%	17% / 6%
Anaemia	55.1% / 0%	70.1% / 1.1%	70.2% / 2.1%
Elevated ALAT	10.3% / 0.5%	18.7% / 1.1%	2.1% / 0%
Elevated ASAT	9.2% / 0.5%	34.2% / 0.5%	4.3% / 0%
Elevated bilirubin	9.7% / 0%	2.7% / 0%	17% / 0%
Cumulated grade 3-5	26%	58%	40%
≥ 1 serious adverse event related to treatment	7%	10%	10%

Mains causes of death	Group 1: N=189 Fluoropyrimidine	Group 1:N=189 FOLFOX /XELOX	Group 2: N=56 Fluoropyrimidine	Group 2: N=57 Observation
Total of all death	**27 (14%)**	**16 (8%)**	**14 (18%)**	**9 (25%)**
Death related to cancer	15 (55%)	8 (50%)	6 (43%)	4 (45%)
Death related to toxicity	0 (0%)	1 (6%)	0 (0%)	0 (0%)
Death of another cause	12 (45%)	7 (44%)	8 (57%)	5 (55%)

Conclusions

- Toxicities of adjuvant chemotherapy are manageable in both groups.
- An early stop of treatment is more frequent in group 2.
- Severe toxicity of fluoropyrimidine are more frequent in group 2 than in group 1.