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RANDOMIZED PHASE III IN ELDERLY PATIENTS COMPARING LV5FU2 WITH OR WITHOUT IRINOTECAN FOR 1ST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER (FFCD 2001-02)

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ABSTRACT

Background : Metastatic colorectal cancer (mCRC) most frequently occurs in elderly patients (pts), but these are less frequently treated with chemotherapy (CT) than younger ones. We report the final results of the first phase III study in elderly pts with mCRC receiving a 5FU-based CT with or without irinotecan.

Methods : Elderly pts (75+) with previously untreated mCRC were randomly assigned to receive a 5FU-based CT, either alone or in combination with irinotecan (FU arms: LV5FU2 or simplified LV5FU2, IRI arms: LV5FU2-CPT11 or FOLFIRI, reduced dosage for cycles 1 and 2). Stratification criteria were: center, Charlson index, Karnofsky index, previous adjuvant CT, sex, age, alkaline phosphatases. Primary endpoint was progression free survival (PFS). 240 events (282 pts) were required to demonstrate an improvement of median PFS from 5.5 to 7.9 months (m) in the IRI arm (bilateral α=5%, β = 80%). Secondary endpoints were overall survival (OS), safety, objective response rate (ORR), QOL and geriatric evaluation. Kaplan-Meier estimation, log-rank tests and Cox model (HR with 95%CI) were used.

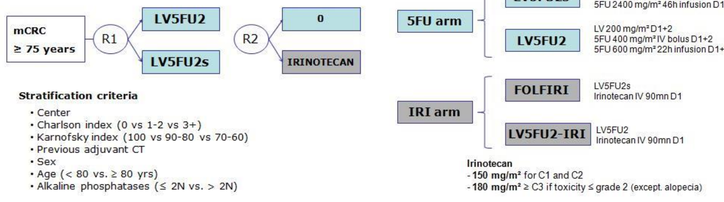
Results : Between 06/2003-05/2010, 142 pts were randomly assigned to FU and 140 to IRI. Median age was similar in both arms 80 years (range 74-92). Main characteristics were well-balanced. Median duration of treatment was 3.5 m in FU and 4.5 m in IRI. At least one CT dose reduction was observed for 30.9% pts in FU and 52.6% pts in IRI. No significant difference was observed for the median PFS: FU 5.2 m vs IRI 7.3 m, HR=0.84 (0.66-1.07), p=0.15. ORR was superior in IRI arm (p=0.002): FU 27.4% (95% CI: 20.1-35.8) vs IRI 46.3% (95% CI: 37.6-55.1). Median OS was 14.2 m in FU vs 13.3 m in IRI , HR=0.96 (0.75-1.24). More patients presented grade 3-4 toxicities in IRI arm (76.3% vs 52.2%), mainly neutropenia (38.5% vs 5.2% of pts), diarrhea (22.2% vs 5.2% of pts) and febrile neutropenia (6.7% vs 0.7% of pts). Toxic deaths occurred in 2 pts in each arm.

Conclusions : In this elderly population, adding irinotecan to an infusional 5FU-based CT seems to increase PFS but does not improve survival and was associated with an increased toxicity.

Introduction

- **CRC is a disease of elderly**
  - Median age at diagnosis: 73 years (SEER)
- **A Public Health problem**
  - US population ≥65 y. : x2 in 2030
  - Suboptimal management
  - No improvement in survival
- **Palliative CT in elderly**
  - Standard regimens not prospectively validated
  - Subgroup analyses, phase II trials suggest feasibility in fit elderly
- **Which optimal regimen in 1st line ?**
  - Tolerance/Efficacy
  - Combination with IRI/OXA or 5FU only ?

Study design



Stratification criteria

- Center
- Charlson index (0 vs 1-2 vs 3+)
- Karnofsky index (100 vs 90-80 vs 70-60)
- Previous adjuvant CT
- Sex
- Age (< 80 vs. ≥ 80 yrs)
- Alkaline phosphatases (≤ 2N vs. > 2N)

Irinotecan
- **150 mg/m²** for C1 and C2
- **180 mg/m²** ≥ C3 if toxicity ≤ grade 2 (except. alopecia)

Main eligibility criteria

- Histologically confirmed unresectable mCRC
- Age ≥75 years
- Karnofsky index ≥60
- Estimated life expectancy > 6 months
- ≥ 1 bi-dimensionally measurable lesion (RECIST)
- No previous CT for metastatic disease
- Adjuvant therapy allowed if stopped at least months before randomization
- Adequate organ and bone marrow function
- Creatinin clearance ≥ 45 ml/mn (Cockroft)
- Signed informed consent

Study endpoints

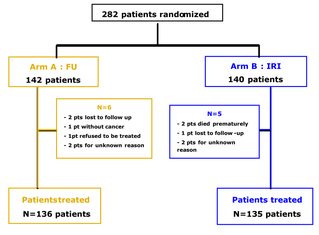
- **Primary endpoint**
  - **Progression-free survival**
    - 5FU arm vs IRI arm
    - as assessed by blinded independent review
    - events : progression or death
- **Secondary endpoints**
  - Overall response rate (independently reviewed)
  - Overall survival (events: deaths all causes)
  - Quality of life (Spitzer scale)
  - Geriatric assessment (IADL, Mini Mental State Examination, Geriatric Depression Scale)
  - Safety
  - Comparison of simplified vs. non simplified regimen

Statistical considerations

- **Assumption for sample size calculation**
  - 240 progressions or deaths (282 pts)
  - increase of median PFS from 5.5 to 8 months in the IRI arm, HR 0.70
  - bilateral 5% type I error, 80% power
- **Final analysis**
  - Kaplan-Meier estimation, log-rank tests and Cox model (HR with 95%CI) were used.

Population

- 06/2003 – 02/2010: 282 pts randomized
- median follow-up: 70 [43- 84] months



Administration

	FU N= 136	IRI N= 135
Treatment administration (months) median (range)	3.5 (0.0-23.6)	4.5 (0.0-23)
Number of cycles – median (range)	8 (1-37)	10 (1-34)
Dose intensity (%) – median (range)		
5FU infusion	97.7 (1.1-186.1)	97.3 (46.7-171.8)
5FU bolus	97.8 (21.6-196.8)	95.3 (7.0-120.5)
Irinotecan	-	93.2 (34.7-177.6)
At least one dose reduction – N(%)	42 (30.9)	71 (52.6)
At least one report – N(%)	80 (58.8)	97 (71.9)

Baseline characteristics

	FU N= 142	IRI N= 140
Age in years		
median (range)	80.4 (74.7-90.4)	80.3 (75.1-91.7)
< 80 years / ≥ 80 years	44.4 /55.6	47.9 / 52.1
Gender - %		
Male / Female	52.8 / 47.2	54.3 /45.7
Karnofsky index - %		
100 / 80-90 / 70-60	14.1 / 54.9 /44	13.6 /55.7 /30.7
Charlson index - %		
0 / 1-2 / 3+	56.3/39.4/4.2	57.9 / 36.4 /5.7
Alkaline phosphatases - %		
≤ 2N / > 2N	78.9 / 21.1	79.3 /20.7
Number of metastatic sites - %	*n=141*	*n=138*
1 / 2 />2	44.0/38.3/17.7	42.0/31.2/26.8
ACE - %	*n=121*	*n=121*
≤ 2N /> 2N	46.3/53.7	47.1 /52.9

Toxicities

- Toxicities on patients with at least one dose of treatment (n=271)

	All grades N (%)		Grades 3-4 N (%)	
	FU N= 136	IRI N= 135	FU N= 136	IRI N= 135
Any toxicity	**135 (99.3)**	**134 (99.3)**	**71 (52.2)**	**103 (76.3)**
Hematological toxicity	**113 (83.1)**	**131 (97.0)**	**10 (7.4)**	**55 (40.7)**
Anemia	103 (75.7)	126 (93.3)	2 (1.5)	7 (5.2)
Neutropenia	31 (22.8)	100 (74.1)	7 (5.2)	52 (38.5)
Febrile neutropenia	1 (0.7)	11 (8.1)	1 (0.7)	9 (6.7)
Non hematological toxicity	**128 (94.1)**	**132 (97.8)**	**66 (48.5)**	**75 (55.6)**
Nausea	57 (41.9)	81 (60.0)	2 (1.5)	9 (6.7)
Vomiting	32 (23.5)	56 (41.5)	2 (1.5)	8 (5.9)
Diarrhea	60 (44.1)	102 (75.6)	7 (5.2)	30 (22.2)
Thromboembolic event	6 (4.4)	17 (12.6)	4 (3.0)	12 (8.9)
Mucositis	32 (23.5)	36 (26.7)	2 (1.5)	2 (1.5)
Myocardial infarction	4 (2.9)	0 (0.0)	4 (3.0)	0 (0.0)

- Toxic deaths occurred in 2 pts in each arm.

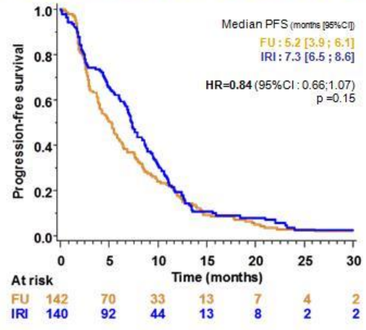
Prognostic factors

- Explanatory multivariate analyses (Cox)

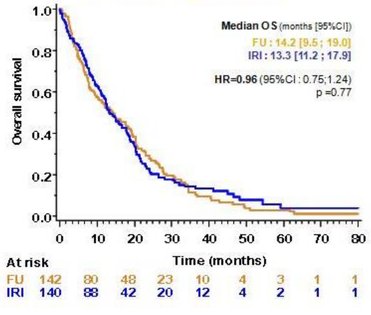
1st model (n=240)	PFS HR	PFS CI95%		PFS p	OS HR	OS CI95%		OS p
Treatment Arm IRI vs FU	0.82	0.63	1.07	0.14	1.06	0.80	1.39	0.70
Alkaline phosphatases ≤2N vs > 2N	0.51	0.36	0.71	**<.0001**	0.37	0.25	0.53	**<.0001**
Number of metastatic sites 1 vs > 2	0.71	0.50	1.00	0.15	0.60	0.42	0.88	**0.03**
2 vs > 2	0.81	0.56	1.16		0.71	0.49	1.04	
ACE ≤2N vs > 2N	0.68	0.49	0.94	**0.02**	0.69	0.49	0.97	**0.03**

2nd model (N=79)	PFS HR	PFS CI95%		PFS p	OS HR	OS CI95%		OS p
Treatment Arm IRI vs FU	0.81	0.48	1.36	0.42	0.90	0.51	1.57	0.70
Alkaline phosphatases ≤2N vs > 2N	0.88	0.45	1.73	0.71	0.66	0.33	1.29	0.22
Number of metastatic sites 1 vs > 2	0.43	0.22	0.84	**0.04**	0.47	0.23	0.97	0.12
2 vs > 2	0.47	0.24	0.93		0.58	0.27	1.24	
ACE ≤2N vs > 2N	0.62	0.36	1.05	0.08	0.51	0.28	0.91	**0.02**
MMSE Score ≤27/30 vs >27/30	0.75	0.45	1.26	0.27	0.94	0.51	1.72	0.83
IADL Score ≤2 vs > 2	0.20	0.06	0.72	**0.01**	0.02	0.005	0.11	**<.0001**
GDS Score ≤2 vs > 2	2.64	1.17	5.97	**0.02**	5.30	2.09	13.42	**0.0004**

Progression free survival



Overall survival



Tumoral response

	FU N=135 N (%)	IRI N=134 N(%)
Objective response rate (CR + PR)	37 (27.4)	62 (46.3)
	OR (95%CI) : 2.3 (1.4-3.8) p=0.001	
CR	5 (3.7)	7 (5.2)
PR	32 (23.7)	55 (41.0)
SD	62 (45.9)	43 (32.1)
PD	26 (19.3)	11(8.2)
NE	10 (7.4)	18 (13.4)

- As estimated by investigators
- RECIST criteria

Conclusion

- Elderly patients can be treated with standard CT regimen with a manageable toxicity
- In this elderly population, adding irinotecan to an infusional 5FU-based CT does not significantly improve PFS and was associated with an increased toxicity.
- Multivariate analysis suggest the importance of geriatric factors as predictive factors of survival