Phase Ⅰ/Ⅱ study CPT-11+UFT/LV in patients advanced Colorectal Cancer.

Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG): Protocol 0303

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Back grounds

Standard first-line chemotherapy in advanced/recurrent colorectal cancer is CPT-11+5-FU/LV(FOLFIRI) or l-OHP+5-FU/LV(FOLFOX).

The other hand, necessary to develop chemotherapy with high convenience . As for UFT/LV, the antitumor effect is similar and side effects is fewer to 5-FU/LV were reported. UFT/LV is more convenient than 5-FU/LV. In the future ,oral fluoropyrimidine(UFT/LV,Capecitabine,etc.) will be expected to replace 5- FU/LV .

We conducted a phase Ⅰ/Ⅱ study of CPT-11+UFT/LV as first line chemotherapy in advanced colorectal cancer to access the maximum tolerated dose(MTD) and recommend dose of CPT-11 when fixed dose UFT/LV,and to evaluate the efficacy and the feasibility of this regimen.

Objectives and endpoints

- **Objectives**
  - To estimate the maximum tolerated dose (MTD) and recommended dose (RD) of CPT-11, when administered in combination with fixed dose UFT/LV for the treatment of advanced colorectal cancer
- **Endpoints**

Primary endpoint : safety and adverse events

Secondary endpoint : antitumor effect

Inclusion criteria

1. Histologically confirmed colorectal cancer
2. At least one measurable or evaluable lesion
3. No previous chemotherapy for advanced or recurrent disease (at least 6months after finishing postoperative adjuvant chemotherapy)
4. No previous radiotherapy
5. Age; 20 - 75
6. Performance status (ECOG) ; 0 - 1
7. Life expectancy ≧ 3 months
8. Adequate organ functions
   - ① WBC : 4,000 – 12,000 /mm³
   - ② Neu ≧ 2,000 /mm³
   - ③ PLT ≧ 100,000 /mm³
   - ④ Hemoglobin : 9.0 g/dL
   - ⑤ GOT・GPT : ＜ ULN x 2.5
   - ⑥ T. Bil : ≦ 1.5 mg/dL
   - ⑦ Creatinine : ≦ULN
9. Written informed consent
10. Able to tolerate oral feeding (oral administration)

Exclusion criteria

1. Case who has interstitial pneumonia or fibroid lung(include previous history)
2. Case who has Coelomic fluid that needs treatment
3. Case with double cancer of briskness. Or, the case to whom a healthy period doesn't come up in five years even if it is different time.
4. Case who has infectious disease and intestines tube paralysis and intestinal obstruction
5. Case who presents diarrhea (watery diarrhea)
6. Defective control example of diabetic syndrome
7. Case who has coexisting illness judged to cause important obstacle to examination enforcement
8. Example of having symptom of brain metastasis syndrome
9. Case who has pregnant woman, breast-feeding woman, and possibility or the will to be pregnant
10. It is a case in the past who has experienced the allergy.
11. Case who judged it is improper to safe execution of examination doctor in charge of examination

Dosage and number of patients

Level	CPT-11 dosage	UFT dosage*	LV dosage	No.
Level0	50mg/m²	300mg/m²/day	75mg/day	3–6
Level1	75mg/m²	300mg/m²/day	75mg/day	3–6
Level2	100mg/m²	300mg/m²/day	75mg/day	3–6
Level3	125mg/m²	300mg/m²/day	75mg/day	3–6
Level4	150mg/m²	300mg/m²/day	75mg/day	3–6

* Dosage of Tegafur

Schedule for dose levels

Numbers of DLT	Schedule
0/3cases	Progress to next dose level.
1/3cases	Addition of up to 3 pts. at the same dose level .
1/6cases	Progress to next dose level.
≧2/3cases or 2/6cases	MTD No more patients are added

Treatment schedule of CPT-11+UFT/LV

4～5weeks(28～35days) of 1course,repeated over 2courses.

Definitions of dose limiting toxicity (DLT) and critical toxicity

- According to NCI-CTC, DLT define as follows;
  - Grade 4 leukopenia, neutropenia
  - Grade 3 thrombocytopenia and Grade 3 non-hematologic toxicity (except nausea and vomiting)
- Critical toxicity define as follows;
  - Cannot administering CPT-11 of day15 of the first course to day21 by the adverse event.
  - Administering days of UFT/LV of the first course (21 days) become less than 14 days by the adverse event.

Patient characteristics

Sex	M/F	9/5
Age (years)	Median	61.0(48–70)
P S	0/1	10/4
Initial/recurrence/unknown		7/4/3
History	wel/mod/por/muc/unknown	5/7/1/0/1
Prior treatment	non/surg/surg+chemo	1/9/4
Metastatic sites	liver/lung/LN/other	10/4/3/2

Non-hematological toxicities (1st course)

	Level 1 (n=3)				Level 2 (n=3)				level 3 (n=3)				Level 4 (n=5)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Diarrhea						1				1				2		1
Abdominal pain						1								2		
Stomatitis	1															
Anorexia	2	1			1				1				1		1	
Nausea	1				2								3	1		
Vomiting					1									1		
Alopecia	1												3			
Fatigue	2				1				1					1		
Constipation	1	1												1		
AST/ALT ↑									1							
T-Bil ↑										1			1			
ALP ↑					1											
K ↓													1			

Hematological toxicities (1st course)

	level 1 (n=3)				Level 2 (n=3)				Level 3 (n=3)				Level 4 (n=5)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Hemoglobin					1				1				2	1		
RBC decrease																
Leukopenia	1								1				1			
Neutropenia		1							1	1			1			
Thrombocytopenia									1							

Summary of DLT

Level	CPT-11 dosage (mg/m²)	DLT
1	75	Non
2	100	Non
3	125	Non
4	150	#4-3 Diarrhea (G3) #4-5 Fatigue (G3)

Response

Level	CPT-11 dosage(mg/m²)	CR	PR	SD	PD	NE	RR (%)
1	75	0	2	1	0	0	66.7
2	100	1	0	1	1	0	33.3
3	125	0	2	1	0	0	66.7
4	150	0	3	2	0	0	60.0
Over all		2	8	3	1	0	57.1

Conclusion

The present study suggests the usefulness of combination chemotherapy with CPT-11 + UFT/LV, which can be performed safely on an outpatient basis with a low incidence of serious adverse events, in the treatment of advanced Colorectal Cancer.

We end the case accumulation by phase Ⅱ study and are analyzing details now. As for an analytical result, it is a report schedule when the future.