Multicentric phase II randomized trial comparing Chemoradiation (CHRT) with 5-fluorouracil, cisplatin (CDDP) and 50 Gy versus chemotherapy alone (CH) with gemcitabine plus oxaliplatin for locally advanced biliary tract cancer (FFCD9902)

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ABSTRACT

Background: No study is available to determine the best strategy for inoperable locally advanced biliary tract cancer. Surgical resection is the standard for limited disease but only a minority of tumors can be removed. CHRT has shown its efficacy in small series to control the local evolution. However CHRT results were compared to palliative CH alone. In our randomized trial safety and efficacy of CHRT and CH have been evaluated. **Methods:** This prospective multicentric phase II trial randomly assigned patients with hilar or extrahepatic non metastatic and locally advanced biliary tract cancer to CHRT (50 Gy plus 5FU infusion 300mg/m²/j, J1 to J33 and CDDP 20mg/m²/j J1 to J4 and J29 to J32 or CDDP 80mg/m² J1 and J29) or to CH alone (gemcitabine 1000 mg/m² J1 + oxaliplatin 100mg/m² J1; J1=J15). Main inclusion criteria required WHO performance status ≤2, bilirubinemia ≤ 50microM/l after biliary drainage if necessary and tumor accessibility to external radiation therapy. Endpoints were progression free survival (PFS), toxicity, rate of biliary complications and overall survival (OS). Stratification was performed according to center, localisation (hilar, extrahepatic and cyst), biliary drainage and PS (0-1 and 2). **Results:** The study was closed before completion of the planned number of patients due to slow accrual. 18 patients and 16 patients were finally included in CHRT and CH arms, respectively. All prognostic factors were well balanced between the two arms (localisation, biliary drainage, bilirubinemia). In CHRT arm, RT, CDDP and 5FU mean cumulative dosages were respectively 86%, 90% and 78% of the theoretical dosages. In CH arm, gemcitabine and oxaliplatin mean cumulative dosages were respectively 70% and 67% of the theoretical dosages. A second line of chemotherapy was given after progression to 55.6% in the CHRT arm and 25% in the CH arm. Most frequent grade 3-4 adverse events respectively for CHRT and CH arms were haematological (23.5% and 25.0%), gastrointestinal (11.8% and 6.2%) and neurological toxicities (0 and 18.7%). Treatment had to be stopped due to toxicity in 1 and 2 patients. Median PFS was 5.8 months in CHRT group and 11.0 months in CH group (HR: 0.65 [0.32-1.33]). Median OS was 13.5 months in CHRT group and 19.9 months in CT group (HR: 0.69 [0.31-1.55]) with a median follow-up of 22.8 months in the CTRT group and 22.5 months in the CT group. Biliary complications, occurred in 27.8% of the patients in CHRT arm and 43.7% of the patients in CH arm (RR: 1.6[0.65-3.9]). It was mainly obstruction (26.7% and 18.2% of the complications by group) or angiocholitis (20.0% and 36.4% of the complications by group). **Conclusion:** Our results suggest that gemcitabine and oxaliplatin chemotherapy is a valuable option in locally advanced biliary tract cancer. Efficacy outcomes seem to be better than CHRT without increase of serious adverse events. Much more patients would be necessary to show a statistical difference

BACKGROUND

Background: No study is available to determine the best strategy for inoperable locally advanced biliary tract cancer. Surgical resection is the standard for limited disease but only a minority of tumors can be removed because non operability or non resecability of the tumor. CHRT has shown its efficacy in small series to control the local evolution. This modality of treatment is currently largely used by practitioners despite its poor benefit assessment. However CHRT results were compared to palliative CH alone. In our randomized trial safety and efficacy of CHRT and CH have been evaluated

METHODS

Primary endpoints : - PFS

Secondary endpoints: - Toxicity (NCI-CTC)
- Biliary complication
- OS

Stratification : Center, localisation (hilar, extrahepatic, cyst), biliary drainage and WHO PS (0-1 vs 2)

Evaluation: - Toxicity NCI-CTC / Week arm A - Toxicity NCI-CTC / 2 Weeks arm B - CT scan / 3 months

Inclusion criteria : WHO Performans Status ≤ 2, Bilirubinemia ≤ 50microM/l
Accessibility to external radiation therapy

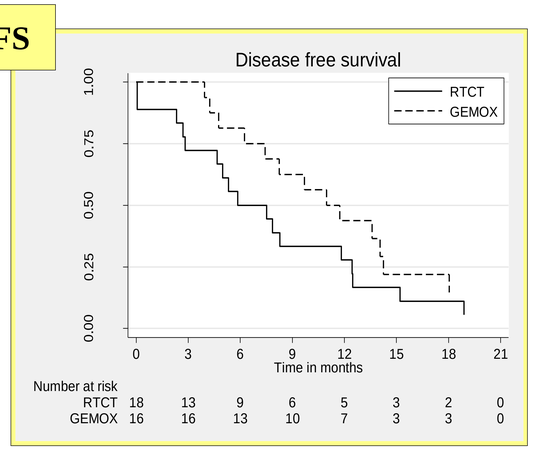
Traitement :

Bras A : - RT 50 Gy
- 5FU 300mg/m²/j J1-J33 and CDDP 20mg/m²/j J1 -J4 and J29-J32 or CDDP 80mg/m²/j J1 and J29

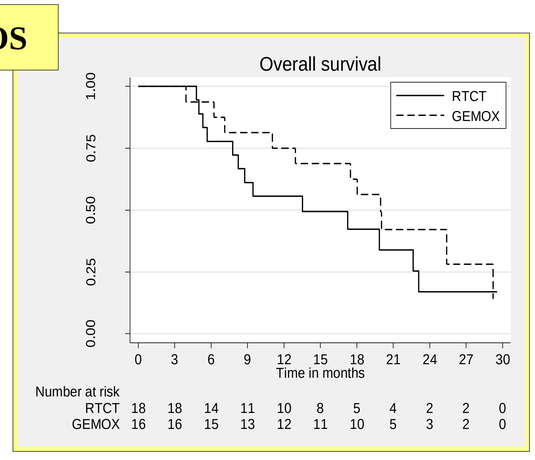
Bras B : - Gemcitabine 100mg/m² J1and Oxaliplatin 100mg/m² J1 J1=J15

RESULTS

PFS



OS



Toxicité Gr 3 - 4

	CHRT	CH
Haematological	23.5%	25.0%
Gastrointestinal	11.8%	6.2%
Neurological	0%	18.7%

Biliary complications

	CHRT	CH
Total	27.8%	43.7%
Obstruction	26.7%	18.2%
Angiocholitis	20.0%	36.4%

CONCLUSION

Our results suggest that gemcitabine and oxaliplatin chemotherapy is a valuable option in locally advanced biliary tract cancer. Efficacy outcomes seem to be better than CHRT without increase of serious adverse events. Much more patients would be necessary to show a statistical difference

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