PHASE I STUDY OF FLUVASTATIN/CELECOXIB COMBINATION IN CHILDREN WITH RELAPSING OR REFRACTORY LOW OR HIGH GRADE GLIOMA FIRST RESULTS

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Introduction

- Preclinical[1,2, 3] and clinical[4] data support the anticancer activity of celecoxib and fluvastatin in high grade (HGG) and low grade gliomas (LGG).
- Phase I trial was designed to evaluate this combination in children with refractory/relapsed HGG and LGG.
- The aims of the study were to assess the safety, maximum tolerated dose and pharmakocinetic in children with recurrent/refractory LGG or HGG

Materiel and Methods

- Multicenter national phase I trial including patients with refractory/relapse HGG or LGG
- Fluvastatin starting dose was 2 mg/kg/day, 14/28 days, with fixed dose of celecoxib (200 mg to 800 mg /day according to weight).
- Four dose levels of fluvastatin (2, 4, 6, 8 mg/kg/day) were planned.
- The dose-escalation scheme was based on a CRML model (Continual Reasssessment Method Likelyhood approach).
- Dose-limiting toxicities (DLT) were determined on the 1st cycle of treatment using the NCI-CTC v4.0 scale.

Results

Patients Characteristics :

20 patients included between June 2014 and August 2018

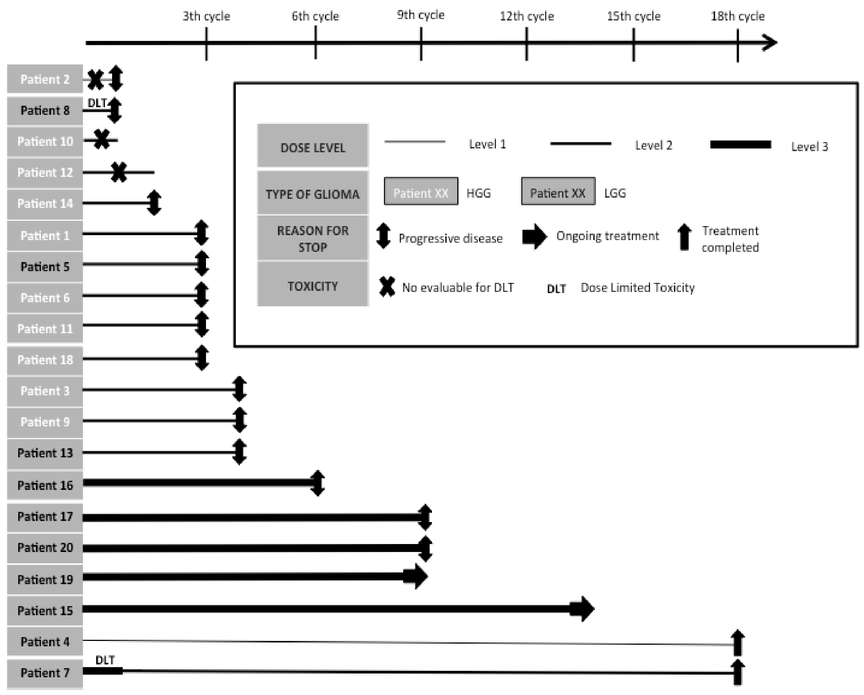
Characteristics	Number (%)
Age	
mediane (extreme)	12.5
max-min	(5.9 ; 19)
Gender	
Male	13 (65)
Female	7 (35)
Neurofibromatosis type 1	3 (15%)
Diagnostic	
Low Grade Glioma	10
High Grade Glioma	10
Grade histologique	
I	5
II	2
III	4
IV	5
unknown	4
Histologic	
astrocytoma pilocytic	6
oligoastrocytome	1
oligodendrogliome	2
astrocytome pilomyxoide	1
others	9
Delay diagnostic-inclusion	
mediane	28.8
max-min	(3.1 ; 172.9)
Anterior treatment	
chemotherapy or target therapy (CT), Radiotherapy (RT) and surgery (S)	11 (55)
CT and S	5 (25)
CT	3 (15)
CT and RT	1 (5)
Localisation	
optico-chiasmatic	5 (25)
hypothalamus	1 (5)
other type	14 (70)
Metastas Statuts	
No	7 (35)
Loco-regional	9 (45)
Metastasis	2 (10)
Loco-regional + metastasis	2 (10)

Evaluation of DLT :

- Seventeen patients were evaluable for DLT
- Two DLTs were reported: 1 grade 3 maculo-papular rash (4 mg/kg) and 1 grade 4 increase of CPK (6 mg/kg).
- No additional grade 3 or more related adverse event was reported during the study.
- The probability of DLT was 9.5% (IC95%: 1.3-28.0%) on level 2, 19.8% (IC95% : 5.0-41.6%) on level 3 ; 36.3% (IC95% : 15.4- 57.8%) on the level 4.

Maximum Tolerated Dose (MTD) was 6 mg/kg/day.

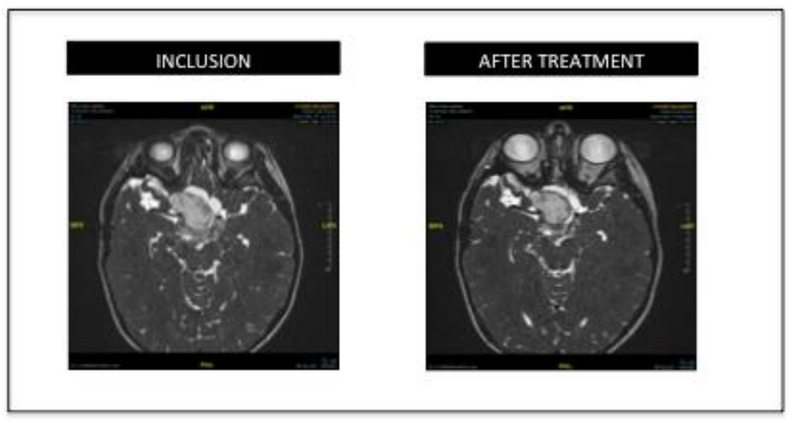
Level dose of fluvastatin received; time on-treatment; type of glioma and reason to stop by patient.



Follow-up (last follow-up July 2019)

- The median duration of treatment was 89 days (range: 4 day–16.6 months)
- The median number of cycles was 8.5 for patient with LGG (1 to 18 cycles) and 3 for patients with HGG (1 to 4 cycles).
- Two patients with LGG received all the 18 cycles of treatment with stable disease.
- Two patients with stable disease were still on treatment at the last follow up (one received 9 cycles and one received 14 cycles).

MRI (T2 gado axial) of patient 16 with LGG at inclusion and after 3 cycles



Summary of fluvastatin pharmacokinetic parameters on Days 1 and 14.

			PK parameters[a]					
	Dose	n	T_{max}[b] (hours)	C_{max} (ng/mL)	AUC_{0-24h} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	$T_{1/2}$ (h)	CL/F (L/h/kg)	V_z/F (L/kg)
D1	2 mg/kg	5	2 (1-5)	1238 ± 1030	2445 ± 1319	2459 ± 1324	4.6 ± 1.5	1.1 ± 0.7	6.5 ± 3.2
	4 mg/kg	7	2 (1-4)	4540 ± 5401	10420 ± 10189	10460 ± 10198	4.1 ± 1.3	1 ± 1	5.5 ± 6.1
	6 mg/kg	1	3	5336	14515	14535	3.7	0.4	2.2
D14	2 mg/kg	5	2	1206 ± 1502	3375 ± 1988		4.8 ± 1	0.8 ± 0.6	5.9 ± 4.4
	4 mg/kg	4	1.5	6220 ± 7769	17367 ± 20413		4.8 ± 1.8	0.7 ± 0.5	2.9 ± 3.2
	6 mg/kg	1	5	4263	13412		4.5	0.5	2.9

[a] mean ± standard deviation. [b] median (range)
T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; AUC_{0-24h}, area under plasma concentration-time curve curve from 0 to 24 hours post-dose; $AUC_{0-\infty}$, area under plasma concentration-time curve extrapolated to infinity; $T_{1/2}$, terminal elimination half-life; CL/F, apparent oral clearance normalized for body weight; V_z/F, apparent oral of volume of distribution during terminal phase normalized for body weight.

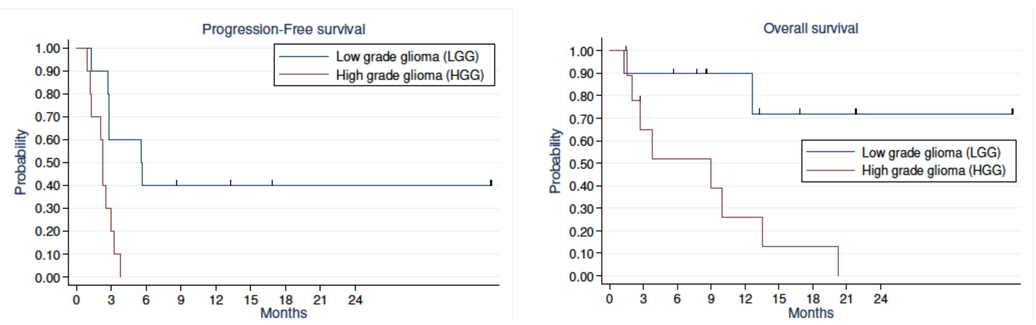
Summary of celecoxib pharmacokinetic parameters on Day 1

			PK parameters[a]						
	Dose	n	Tmax[b] (hours)	Cmax (ng/mL)	AUC_{0-12h} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	$T_{1/2}$ (h)	CL/F (L/h/kg)	V_z/F (L/kg)
D1	200 mg	6	3.5 (2-4)	1475 ± 430	7577 ± 2032	11065 ± 4222	6 ± 3	0.6 ± 0.5	4.2 ± 1.9
	400 mg	7	4 (3-8)	1351 ± 317	7378 ± 2228	10696 ± 3631	6 ± 3	0.6 ± 0.2	5.0 ± 2.4

PK data are consistent with previous results reported in children which reported a high inter-individual variability. The results of the PK sub-study showed no significant interaction between fluvastatin and celecoxib

Conclusion

- **In children with refractory/relapsed glioma, the MTD of fluvastatin associated with celecoxib is 6 mg/kg/day.**
- **This combination displayed a very limited toxicity with interesting preliminary activity in LGG encouraging a phase 2 study or its use as a maintenance in children with LGG.**



Kaplan–Meier curves for PFS and OS according to the type of glioma.

References : (1) Sato A, Mizobuchi Y, Nakajima K et al. Blocking COX-2 induces apoptosis and inhibits cell proliferation via the Akt/survivin- and Akt/ID3 pathway in low-grade-glioma. J Neurooncol. 2017 Apr;132(2):231-238. (2) Sławińska-Brych A, Zdzisińska B, Kandefer-Szerszeń M. Fluvastatin inhibits growth and alters the malignant phenotype of the C6 glioma cell line. Pharmacol Rep. 2014 Feb;66(1):121-9. (3) Mercurio S., Padovani L., Colin C. et al. Evidence for new targets and synergistic effect of metronomic celecoxib/fluvastatin combination in pilocytic astrocytoma. Acta Neuropathol Commun 2013; 1: 17. (4) López-Aguilar E, Sepúlveda-Vildósola AC, Rivera-Márquez H, Cerecedo-Diaz F, Valdez-Sánchez M, Villasis-Keever MA. Security and maximal tolerated doses of fluvastatin in pediatric cancer patients. Arch Med Res. 1999 Mar-Apr;30(2):128-3