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Utilisation du sorafénib en situation néo-adjuvante pour carcinome hépatocellulaire en attente de transplantation hépatique

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AVERTISSEMENT

La faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celle- ci sont propres à leurs auteurs.

List of abbreviations

AE: Adverse event
AFP: Alpha-fetoprotein
CMV: Cytomegalovirus
CI: Confidence interval
CR: Complete response
CT : Computerized tomography
DO: Drop-out
HAT: Hepatic artery thrombosis
HCC: Hepatocellular carcinoma
HFS: Hand-foot syndrome
LRT: Loco-regional therapy
LT: Liver transplantation
MELD: Model for End-stage Liver Disease
MRI: Magnetic Imaging Resonance
OS: Overall survival
PBC: Primary biliary cholangitis
PD: Progressive disease
PR: Partial response
RFA: Radiofrequency ablation
SCH: Subcapsular hematoma
SD: Stable disease / Standard deviation
SMV: Superior mesenteric vein
So: Sorafenib
TACE: Transarterial chemoembolization
TARE: Transarterial radioembolization

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RESUME

Contexte : Les données portant sur l'efficacité et la sécurité du Sorafenib (So) en situation néo-adjuvante pour CHC en attente de transplantation hépatique (TH) sont hétérogènes et rares. Notre étude avait pour objectif de décrire l'histoire naturelle des patients traités par So en attente de TH.

Patients et méthodes : Tous les patients inscrits sur liste entre mai 2010 et avril 2019 et traités par So en attente de TH ont été inclus. Une évaluation clinique et biologique était réalisée tous les mois. Une évaluation de la réponse radiologique tumorale selon mRECIST était entreprise de façon trimestrielle sur liste d'attente et semestrielle après TH.

Résultats : 327 patients ont été inscrits sur liste d'attente de TH pour CHC, parmi lesquels 62 (19%) étaient traités par So. Il s'agissait dans 82% des cas d'hommes âgés de 59 ans avec une cirrhose alcoolique dans 81% des cas. Le So était initié pour progression tumorale après traitement locorégional dans 50% des cas et pour impossibilité d'autres traitements dans 50% des cas. La durée moyenne de traitement était de 6 mois avec une posologie moyenne de 585 mg/jr. Trente-six (58%) patients sont sortis de liste pour progression tumorale et 26 (42%) patients ont été transplantés. Une réponse objective radiologique était obtenue chez 27% des patients transplantés versus 0% chez les patients sortis liste. Sept récidives (27%) ont été identifiées après un suivi moyen de 24 mois après TH. Les facteurs indépendants prédictifs de récidive étaient l'étiologie de la cirrhose et le dernier score AFP avant TH. La survie globale post-TH à 5 ans était de 77% et la survie sans récidive de 48%.

Conclusion : Le So a permis de maintenir un projet de TH pour 42% des patients considérés en impasse thérapeutique sur liste pour CHC. La survie sans récidive à 5 ans est inférieure à l'objectif actuel dans cette indication. Le dernier score AFP avant TH est un élément essentiel à prendre en considération.

SUMMARY

Background: Data on efficacy and safety of Sorafenib (So) in the neoadjuvant setting for HCC awaiting liver transplantation (LT) are heterogeneous and scarce. We aimed to investigate the natural history of patients treated with So while awaiting LT.

Methods: All patients listed for HCC between May 2010 and April 2019 and treated with So awaiting LT were included. A clinical and biological evaluation was performed every month. Radiological tumor response evaluation according to mRECIST was realized every three months on the waiting list and every six months after LT.

Results: 327 patients were listed for HCC, of which 62 (19%) patients were treated with So. Patients were men aged 59 in 82% of cases and had alcohol-related cirrhosis in 81% of cases. So was initiated for tumor progression after locoregional treatment in 50% of cases and for impossibility of other treatments in 50% of cases. The mean duration of treatment was 6 months with a mean dose of 585 mg/d. 36 (58%) patients dropped-out for tumor progression and 26 (42%) patients were transplanted. An objective radiological response was achieved in 27% of transplanted patients versus 0% of patients who dropped-out. Seven recurrences were identified after a mean follow-up of 24 months after LT. The independent factors predictive of tumor recurrence were principal etiology of cirrhosis and last AFP score prior to LT. The 5-year overall survival after LT was 77% and the 5-year recurrence-free survival was 48%.

Conclusion: So as neoadjuvant rescue therapy provided access to LT for 42% of patients. Recurrence-free survival at 5 years is below the current target in this indication. The last AFP score before LT is an essential element to take into consideration.

I. Introduction

Primary liver cancer is the 6th most common cancer and represents the 4th leading cause of cancer death worldwide with 841,000 new cases and 782,000 deaths in 2018 (1). Hepatocellular carcinoma (HCC) is the most common primary tumor, accounting for 75 to 85% of primary liver tumors. In France, the standardized incidence rate of HCC is 16,4 per 100,000 persons per year (2). An 85% increase in incidence has been observed over the last 40 years. Projections suggest that the increase in incidence will continue with 12,000 new cases expected in 2030 (3). Despite recent therapeutic advances, the prognosis of HCC remains among the worst of all cancers with a median survival of 9,4 months and a 5-year survival of 9,6% (2).

Liver Transplantation (LT) is the only therapy that, unlike other curative treatments (ablative therapies, surgical resection), simultaneously cures the tumor and the underlying liver disease. However, few patients are eligible for LT because of their condition (age, comorbidities), behavior (observance, abstinence in alcohol consumption) and their tumor biology and spread. The eligibility of LT in France is based on the alpha-fetoprotein (AFP) score which includes the number of nodules, their size, and the AFP level. The access to LT is mainly based on the time spent on the waiting list. According to the Agence de la Biomédecine, HCC is currently the leading indication for LT in France, accounting for 30% of registrations on the waiting list. The main problem related to LT is donor shortage. Indeed, the number of candidates for an available graft is 2,4. This shortage imposes a waiting time before LT which may lead to tumor progression beyond accepted criteria. Median waiting time for patients enrolled in the HCC component is 12 months (56% access at 12 months and 74% at 24 months) (4).

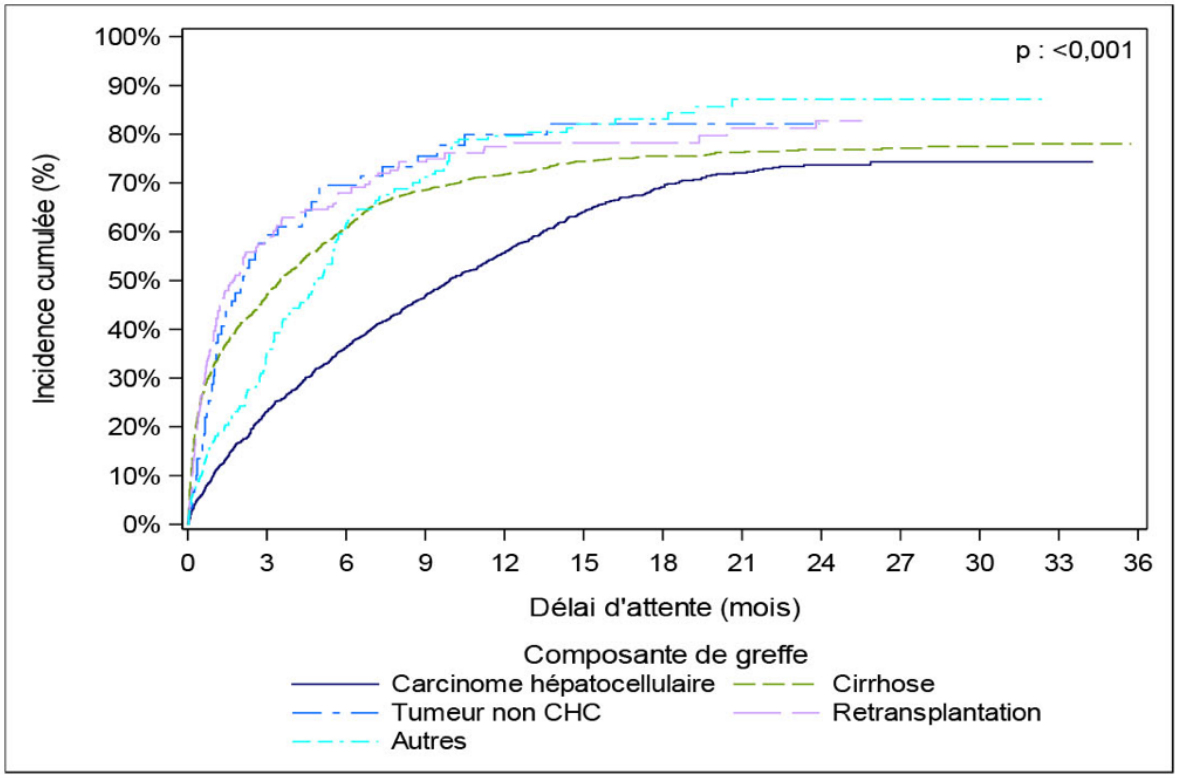


Figure 1 Cumulative incidence rate of transplant and death or worsening on the liver transplant waiting list by component of liver score in the active list (2017-2018).

Strategies to minimize or avoid waitlist dropout related to tumor progression include loco-regional therapy (LRT). Indeed, transarterial modalities (transarterial chemoembolization—TACE, transarterial radioembolization—TARE) and percutaneous thermal ablative strategies (radio frequency ablation—RFA, microwave ablation) have been widely adopted by transplant programs to bridge HCC candidates before LT. The choice of treatment type is determined by the size, number, and location of the nodule(s), liver function, and individual center experience. A consensus statement for LT for HCC has recommended LRT if the anticipated waiting time for an organ to become available exceeds 6 months (5). By limiting the risk of progression on the waiting list, LRT also reduces the risk of recurrence after LT, especially when a partial or complete response according to mRECIST is achieved before transplantation (6–8). Other prognostic factors such as low AFP level, low number of tumor nodules

and small total tumor diameter at baseline, extended post-interventional tumor necrosis, well differentiated tumor grade and lack of microvascular invasion have been shown to reduce posttransplant tumor recurrence (9). Tumor recurrence is the main cause of mortality after LT for HCC with a 5-year survival of 22% in case of recurrence (10). It is therefore crucial to optimize management of patients awaiting LT to improve their long-term prognosis.

Sorafenib (So) is a multikinase inhibitor with activity against Raf kinase and several receptor tyrosine kinases, including vascular endothelial growth factor receptor 2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), FLT3, Ret, and c-Kit. So has a dual mechanism of action by targeting both the tumor cell directly (inhibition of cell proliferation, notably through the Raf signaling pathway) and the endothelial cells of blood vessels (inhibition of angiogenesis through the VEGF and PDGF signaling pathway) (11). It was the first systemic therapy to prolong survival in patients with advanced HCC, suggesting that its use in the neoadjuvant setting may be beneficial (12). However, there remains a concern that So's anti-angiogenic effect may interfere with tissue repair and thus lead to increased post-transplant complications. Data on efficacy and safety of So in this setting are heterogeneous and scarce so far (13–18).

We sought to analyze in a large cohort of patients treated with So as neoadjuvant therapy for HCC:

1) Natural history and trajectory of patients awaiting LT treated with So (dropout rate for progression, tolerance, radiological response to treatment)
2) Peri-operative morbidity
3) Overall (OS) and recurrence-free survival after LT

II. Patients and methods

a. Study characteristics and population

This single-center, non-randomized, retrospective, and observational study was performed at the Lille University Hospital.

We investigated all HCC patients listed for LT between May 2010 and April 2019 and treated with So for at least one day on the waiting list. Patients were selected from the nationwide CRISTAL registry. Diagnosis of HCC was established by pathological analysis of directed biopsies or according to the non-invasive criteria of the European Association for the Study of the Liver (EASL) guidelines (19). Each indication of LT was submitted to validation of a multidisciplinary liver conference, which included at least a liver surgeon, a hepatologist, an oncologist and a radiologist specialized in LT.

All patients had measurable disease parameters that had been classified according to mRECIST (modified Response Evaluation Criteria in Solid Tumours) with no evidence of radiologically definable major vascular invasion or extrahepatic metastases. Study flow chart is presented in Figure 2.

b. Indication and management of Sorafenib

So was initiated in two different cases: in case of tumor progression after failure of TACE, or in case of impossibility of another loco-regional procedure (multifocal tumor or technical impossibility). So was mainly introduced to prevent drop-out but could also be introduced to achieve tumor downstaging by reducing tumor burden for patients initially outside eligibility criteria (AFP score > 2). Patients started treatment

either at 400 mg twice a day (full dose) or at 200 mg twice a day with escalation at full dose in case of good liver function and absence of side effects.

c. Follow-up awaiting LT

Liver transplant waiting list time was defined as the number of days from the time of activation on the liver transplant waiting list until the day of transplantation. Physical examination, adverse events and laboratory monitoring including biochemical and hematological parameters were carried out every month. MELD and AFP score were calculated at each visit. Dose modifications, temporary treatment pauses, and symptomatic treatments were prescribed depending on side effects which were graded using the National Cancer Institute's Common Terminology Criteria for adverse events. In case of a grade 2 adverse event, treatment was reduced to half dose and the patient was reassessed on day 15. In case of a grade 3 side effect, treatment was discontinued. Treatment was continued until the day of transplantation or until tumor progression.

Contrast-enhanced CT-scan or MRI was performed at baseline and repeated every three months. Radiological tumor response during treatment with So was assessed according to mRECIST (20). Complete response (CR) was defined as the absence of arterially enhanced areas in all target lesions; partial response (PR) and progressive disease (PD) as a greater than 30 % decrease and a greater than 20 % increase, respectively, in the sum of the longest diameters of arterial enhanced areas in all target lesions; and SD as neither PR nor PD. Radiological assessment of tumor characteristics (number of nodules, maximum nodule diameter and sum of all diameters) was collected retrospectively on last imaging preceding So introduction and on final pretransplant or prior to DO imaging.

d. Explant histopathology examination

All liver explants were examined by an experienced hepatopathologist. Tumor characteristics, gross appearance (nodular or infiltrative), extent of tumor necrosis, vascular invasion, cell differentiation and presence of satellite nodules were analyzed.

e. Peri-operative morbidity and follow-up

Peri-operative complications including incidences of surgical revision, sepsis, hemorrhage, vascular thrombosis, overall bile duct complication and bile duct stenosis, asymptomatic CMV infection, pathologically confirmed acute cellular rejection and re-transplantation were reported. Blood loss until the 1st month after LT and length of patient's hospital stay were collected. Occurrences of HCC tumor recurrence after LT and OS were also identified.

Post-transplant monitoring was adapted to date of LT and included 6-monthly contrast-enhanced CT-scan or MRI imaging coupled with AFP measurements during the first 5 years of follow-up, then annually during 5 additional years. The database was fixed on March 2021 for the last news.

f. Statistical analysis

Demographic (age, gender), clinical (underlying liver disease, type of LRT preceding listing, waiting list time), carcinologic (AFP score), laboratory (MELD-score, AFP level and AFP score at listing), explant tumor characteristics and radiologic variables (tumor characteristics, Milan criteria) were registered. HCC recurrence free survival events were censored at the date of death or HCC recurrence. Continuous

variables were summarized as means and standard deviation (SD) or medians and 95% Confidence Intervals (CI). Comparisons of categorical and continuous variables were performed using the Chi-square test and the Mann–Whitney U-test, respectively. OS and recurrence-free survival rates were determined according to the Kaplan-Meier method. Patient survival in different groups was compared using the log-rank test. Survivals were expressed as percentage ± SD. Predictors for HCC recurrence free survival were analyzed using a multivariate analysis applying a logistic regression. A p value of 0,05 or less was considered statistically significant. All statistical analyses were performed using NCSS version 9.

III. Results

a. Patient characteristics at listing

During the period of May 2010 to April 2019, 327 HCC candidates were listed for LT. Of these patients, 62 (19%) were treated with So awaiting LT, among them 26 (42%) underwent LT and 36 (58%) dropped-out from the waiting list for tumor progression. Patient main characteristics are presented in table 1. The majority of patients were middle-aged men and had compensated alcohol-related cirrhosis. There were no significant differences in demographic characteristics or therapeutic management prior to listing among the 2 groups, transplanted group (LT) and drop-out group (DO).

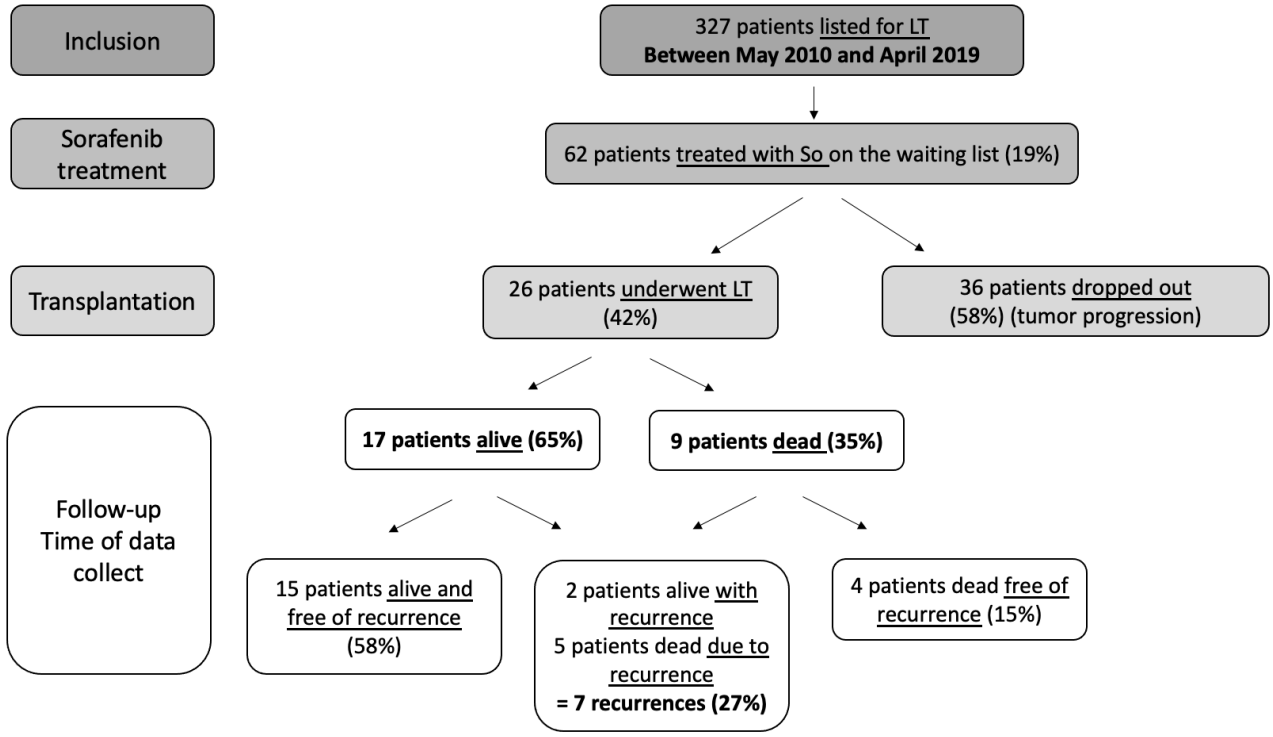


Figure 2. Flow chart

Table 1. Patient characteristics at listing

	n	Total cohort n=62	LT n=26	DO n=36	p
Age (years) **Mean** ± SD **Median** (CI 95%)	62	59 ± 7,9 61,2 (CI95% :58,3-62,2)	57 ± 9,7 61 (CI95% :56,7-62,1)	60,5 ± 5,9 61,5 (CI95% :58,1-63)	NS
Gender, M/F, n (%)	62	51 (82,3%) / 11 (17,7%)	20 (76,9%) / 6 (23,1%)	31 (86,1%) / 5(13,9%)	NS
Etiology of cirrhosis, n (%) Alcohol Viral Metabolic Hemochromatosis PBC Non cirrhotic liver	62	 50 (80,7%) 5 (8,1%) 3 (4,8%) 1 (1,6%) 1 (1,6%) 2 (3,2%)	 20 (76,9%) 1 (3,9%) 2 (7,7%) 1 (3,8%) 1 (3,8%) 1 (3,8%)	 30 (83,3%) 4 (11,1%) 1 (%) 0 0 1 (2,8%)	NS

MELD **Mean** ± SD **Median** (CI 95%)	62	 10 ± 3,9 9 (CI95% :8-10)	 9,9 ± 3,2 9 (CI95% :8-11)	 10,1 ± 4,4 8,5 (CI95% :7-11)	NS
Treatment before listing, n (%) None TACE alone Surgery alone RFA alone **Combinations** 2 lines 3 lines 4 lines	62	 14 (22,6%) 22 (35,5%) 8 (12,9%) 6 (9,7%) 8 (12,9%) 3 (4,8%) 1 (1,7%)	 8 (30,8%) 8 (30,8%) 4 (15,4%) 1 (3,9%) 3 (11,5%) 1 (3,9%) 1 (3,9%)	 6 (16,7%) 14 (38,9%) 4 (11,1%) 5 (13,9%) 5 (13,9%) 2 (5,6%) 0	NS

b. Patient management on waiting list

Approximately two-thirds of the total cohort (66,7%) received at least one TACE treatment on the waiting list. Treatment indication is presented in table 3. Half of the total cohort started So for tumor progression and the other half started So because of impossibility of TACE. There was a significant difference between the two groups in terms of treatment indication. Most transplanted patients initiated So because of impossibility of TACE and most patients who dropped-out initiated treatment because of tumor progression. Mean and median waiting time were respectively 13±4,5 months and 12,5 months (CI 95% 11,2-14,3) from listing to LT, and respectively 10,4±5,4 months and 8,3 months (CI 95% 6,8-11,7) from listing to drop-out or death.

c. Tumor characteristics at listing

HCC characteristics are presented in table 2. Approximately one third of patients had one nodule, one third had two nodules and one third had at least three nodules.

Patients who dropped-out of the waiting list tended to have a larger maximum tumor diameter than transplanted patients (29,5 vs 22,9, p= 0,08) and fewer nodules (p=0,07). Mean AFP-level was 47,4±123 UI/L. Four patients were listed beyond eligibility criteria and treated with So in order to achieve tumor downstaging.

Table 2. Tumor characteristics at listing

	n	**Total cohort n=62**	**LT n=26**	**DO n=36**	**p**
Tumor number **Mean** ± SD **Median** (CI 95%)	62	 2,2 ± 1,3 2 (CI 95% : 2-2)	 2,5 ± 1,5 2 (CI 95% :1-3)	 2 ± 1 2 (CI 95% : 1-2)	NS
Maximum tumor diameter **Mean** ± SD (mm)	62	 26,7 ± 16,5	 22,9 ± 8,2	 29,5 ± 20,2	0,08
Total tumor diameter **Mean** ± SD (mm)	62	 46,4 ± 27,3	 45,1 ± 22,1	 47,4 ± 30,8	NS
Number of nodules, n (%) 1 nodule 2 nodules 3 nodules > 3 nodules	62	 21 (33,9%) 23 (37,1%) 9 (14,5%) 9 (14,5%)	 8 (30,8%) 6 (23,1%) 7 (26,9%) 5 (19,2%)	 13 (36,1%) 17 (47,2%) 2 (5,6%) 4 (11,1%)	0,07
Largest nodule, n (%) <30 mm ≥30 mm **Unique tumor,** n (%) ≤30 mm >30 mm	62 62	 44 (71%) 18 (29%) 18 (29%) 3 (4,8%)	 20 (76,9%) 6 (23,1%) 6 (23,1%) 2 (7,7%)	 24 (66,7%) 12 (33,3%) 12 (33,3%) 1 (2,8%)	NS NS

AFP-level (UI/L): **Mean** ± SD **Median** (CI 95%)	62	 47,4 ± 123,7 8 (CI 95% 6-13)	 50,7 ± 126,1 6 (CI 95% :4-11)	 45,1 ± 123,7 11 (CI 95% :7-21)	NS
Milan criteria fulfilled, n (%) Yes / No	62	 43 (69,4%) / 19(30,7%)	 18 (69,2%) / 8 (30,8%)	 25 (69,4%) /11 (30,6%)	NS
AFP score, n (%) 0 1 2 3 4	62	 38 (61,3%) 8 (12,9%) 12 (19,4%) 3 (4,8%) 1 (1,6%)	 14 (53,9%) 3 (11,5%) 8 (30,8%) 1 (3,9%) 0	 24 (66,7%) 5 (13,9%) 4 (11,1%) 2 (5,6%) 1 (2,8%)	NS

d. Tolerance and treatment management of So

So was discontinued in 71% of all patients, mainly for hepatic decompensation in the LT group and mainly for tumor progression in the DO group. Sixty-nine % of the transplanted patients had continued So until LT. In the total cohort, So was initiated at a mean dose of 585,2 mg and continued for a mean duration of 6 months, with no significant differences between the LT and the DO group. Gastrointestinal disorders tended to be more frequent in the LT group than in the DO group (p= 0,07).

Table 3. Tolerance and treatment management of So

	n	Total cohort	n	LT	n	DO	p
Treatment indication, n (%)	62		26		36		**0,01**
Tumor progression		31 (50%)		8 (30,8%)		23 (63,9%)	
Impossibility of TACE		31 (50%)		18 (69,2%)		13 (36,1%)	
Treatment withdrawal, n (%)	61	42 (71%)	26	8 (30,8%)	35	34 (97,1%)	**<0,0001**
Reason for withdrawal, n (%)	42		8		34		
Intolerance		5 (11,9%)		0		5 (14,7%)	**0,009**
Tumor progression		22 (52,4%)		1 (12,5%)		21 (61,8%)	
Hepatic decompensation		13 (31%)		6 (75%)		7 (20,6%)	
Fatigue		2 (4,8%)		1 (12,5%)		1 (%)	
Mean So treatment time ± SD (months)	62	6 ± 7	26	8 ± 10	36	4,6 ± 3	NS
Mean start dose ± SD (mg)	61	585,2 ± 218	25	616 ± 215,4	36	563,9 ± 221,9	NS
Dose reduction, n (%)	61	25 (41%)	25	11 (44%)	36	14 (38,9%)	NS
Aggravation at 1 month after introduction n (%)	62	13 (21%)	26	5 (19,2%)	36	8 (22,2%)	NS
Adverse events, n (%)	62		26		36		
HFS / skin injury		26 (41,9%)		13 (50%)		13 (36,1%)	NS
Fatigue		13 (21%)		5 (19,2%)		8 (22,2%)	NS
Hematological toxicity		2 (3,2%)		1 (3,9%)		1 (2,8%)	NS
Liver decompensation		10 (16,1%)		5 (19,2%)		5 (13,9%)	NS
Gastrointestinal disorders		23 (37,1%)		13 (50%)		10 (27,8%)	0,07
Digestive bleeding		4 (6,5%)		1 (3,9%)		3 (8,3%)	NS
Hypertension		2 (3,2%)		2 (7,7%)		0	NS
Neuropathy		1 (1,6%)		0		1 (2,8%)	NS
So at time of LT, n (%)	26	-		18 (69,2%)		-	NA

e. Radiologic assessment prior to LT or DO

Maximum mean and median tumor diameter prior to LT or DO was significantly higher in the DO group than in the LT group (p = 0,002). Last mRECIST radiological response prior to LT or drop-out is detailed in table 4. Of the total cohort, 48,4% achieved disease control and 11,3% achieved objective response.

Table 4. Tumor characteristics and last radiological tumor response prior to LT or DO

	n	**Total cohort**	**n**	**LT**	**n**	**DO**	**p**
Sum of largest diameters (LD) (mm): **Mean** ± DS **Median** (CI 95%)	58	 65 ± 43 56 (46-63)	26	 52 ± 28 50 (32-66)	32	 75 ± 50 60 (36-100)	NS
Maximum tumor diameter (mm): **Mean** ± DS **Median** (CI 95%)	58	 32,7 ± 25 25 (20-32)	26	 22,1 ± 11 20 (17-25)	32	 41,3 ± 29 35 (25-40)	**0,002**
Last mRECIST radiological response, n (%) CR PR SD PD	62	 1 (1,6%) 6 (9,7%) 23 (37,1%) 32 (51,6%)	26	 1 (3,9%) 6 (23,1%) 12 (46,2%) 7 (26,9%)	36	 0 0 11 (30,6%) 25 (69,4%)	**0,001**

f. Explant histopathology analysis

Pathological examination exposed in table 5 showed that most explants had ≥ 4 nodules (76%) which contained minimal necrosis (56,3%), no satellite nodules (75%) and no microvascular (80%) or macrovascular (96%) invasion. Most tumors were well-differentiated (64%) and not infiltrative (92%).

Table 5. Explant pathologic characteristics

	n	**LT**
Largest diameter, mean (mm) ± SD	25	24,9 ± 11
Sum of diameter, mean (mm) ± SD	23	61,3 ± 32,5
Tumor number, n (%)	25	
1 nodule		3 (12%)
2 or 3 nodules		3 (12%)
≥ 4 nodules		19 (76%)
Extent of tumor necrosis, n (%)	16	
Complete (no viable tumor) (100%)		1 (6,3%)
Subtotal necrosis (≥90%)		1 (6,3%)
Partial necrosis (≥ 50% and <90%)		3 (18,8%)
Minimal necrosis (<50%)		9 (56,3%)
No necrosis (0%)		2 (12,5%)
Differentiation grade, n (%)	25	
Well differentiated		16 (64%)
Moderately and poorly differentiated		8 (32%)
Not applicable (complete necrosis)		1 (4%)
Infiltrative HCC, n (%)	25	2 (8%)
Satellite nodules, n (%)	16	4 (25%)
Microvascular invasion, n (%)	25	5 (20%)
Macrovascular invasion, n (%)	25	1 (4%)

g. Post-LT morbidity

Post-transplant complications are presented in table 6. Median length of hospital stay was 19,5 days. Eight patients underwent revision surgery (30%), of which four were related to bleeding episodes, two to bowel dehiscence, one to bile leakage and one to wall abscess. Seven bleeding episodes occurred (27%), of which four were graft hematomas, one wall hematoma, one digestive ulcer and one hemoperitoneum. Bile duct stenosis concerned three patients (11%), of which two were treated endoscopically and one required no specific management because of the absence of biological repercussions. Two patients presented with bile leakage. Vascular thrombosis occurred in seven patients (27%) and are detailed in table 6. One patient underwent re-transplantation for severe ischemic cholangitis related to hepatic artery thrombosis. Acute rejection occurred in four patients. Rejection episodes were moderate for three patients and severe for one patient.

One patient had a severe complication. During declamping, the patient presented hemodynamic instability requiring the introduction of noradrenaline. At wound closure, the patient presented a hypertensive peak with tachycardia, followed by severe hypotension and cardiac arrest. Post-arrest (no flow 0, low flow 3 minutes), cardiac echocardiography showed biventricular failure. Thoracic angioscanner showed a sub-segmental pulmonary embolism which did not explain the severity of the clinical condition. Brain scan and coronary angiography did not show any lesion. Due to the persistence of the cardiac failure, ECMO was implemented. The episode was resolutive and no other cardiovascular complications were noted.

Table 6. Post-transplant complications

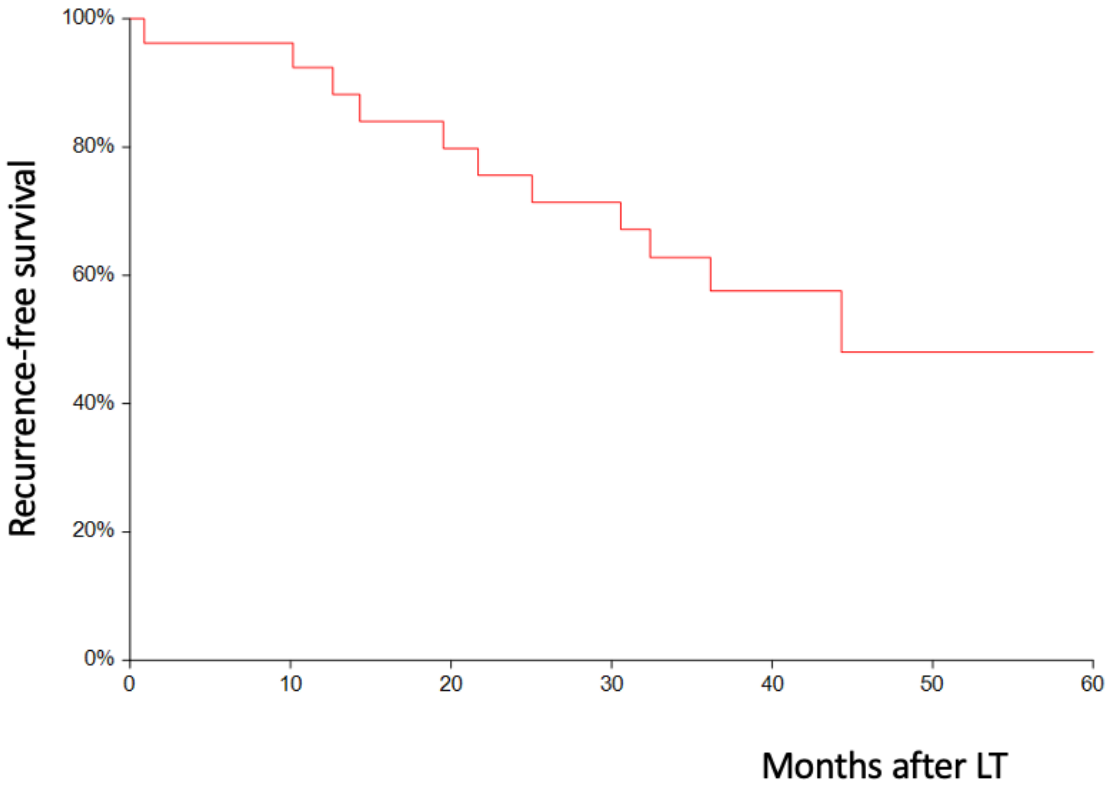
	n	LT
Length of hospital stay (days) **Mean** ± SD **Median** (CI 95%)	26	 26,5 ± 17,6 19,5 (CI 95% 16-24)
Revision surgery, n (%) Bleeding Bowel dehiscence Bile leakage Wall abscess	26	8 (30,8%) 4 2 1 1
Bleeding, n (%) Graft hematoma (SCH/subhepatic) Wall hematoma Digestive ulcer Hemoperitoneum	26	7 (26,9%) 4 (1/3) 1 1 1
Number of peri-operative packed red blood cells **Mean** ± SD **Median** (CI 95%)	25	 4,8 ± 6,5 3 (CI 95% 1-5)
Bile duct stenosis, n (%)	26	3 (11,5%)
Thrombosis, n (%) Hepatic artery thrombosis Pulmonary embolism Portal / SMV thrombosis Renal vein thrombosis	26	7 (26,9%) 3 (11,5%) 1 (3,8%) 2 (7,7%) 1 (3,8%)
Asymptomatic CMV infection, n (%)	26	10 (38,5%)
Re-transplantation, n (%)	26	1 (3,9%)
Acute rejection, n (%)	26	4 (15,4%)
Sepsis, n (%)	26	9 (34,6%)

h. Recurrence and survival

Seven transplanted patients (27% of the LT group) experienced HCC recurrence, which was intrahepatic only for one patient, intrahepatic and extrahepatic for one patient, and extrahepatic for five patients. Extrahepatic tumor recurrence occurred as lung metastases in four patients and lymph nodes metastases in two

patients. The mean time to recurrence was 24,7±9 (13-36) months. The five-year recurrence-free survival among the transplanted patients was 48%±12% (figure 3).

Figure 3. Estimated recurrence-free survival after LT according to Kaplan-Meier



Demographic, clinical, radiological and explant features were modeled in a univariate analysis to identify factors predicting HCC recurrence after LT and are summarized in table 7. Lower tumor number and lower total tumor diameter at listing correlated significantly with higher recurrence rate (p=0,003 and p=0,002 respectively). HCC recurrence rate was reduced significantly in patients fulfilling Milan criteria at listing (p=0,039) and in patients which AFP score prior to LT was ≤ 2 (p=0,01). No histopathological factors were significantly associated with HCC recurrence free survival.

Table 7. Univariate analysis of risk factors for HCC recurrence after LT

	n	No recurrence	Recurrence	p
Age (years) **Mean** ± SD **Median** (CI 95%)	26	 56,3 ± 10,2 60,3 (CI95% 54,1-62,2)	 58,7 ± 8,6 61,4 (CI95% 40,3-67,4)	 NS
Gender, n (%) Male Female	26 20 6	 15 (75%) 4 (66,7%)	 5 (25%) 2 (33,3%)	 NS
Principal etiology of cirrhosis, n (%) Alcohol Viral Metabolic Other *-Hemochromatosis* *-PBC* *-Non cirrhotic liver*	26 20 1 2 3	 17 (85%) 1 (100%) 1 (50%) 0	 3 (15%) 0 1 (50%) 3 (100%)	 **0,026**
MELD at listing **Mean** ± SD **Median** (CI 95%)	26	 10,5 ± 3,5 10 (CI95% 7-13)	 8,4 ± 1,6 9 (CI95% 6-11)	 NS
Tumor number at listing **Mean** ± SD **Median** (CI 95%)	26	 3 ± 1,5 3 (CI95% 2-3)	 1,3 ± 0,8 1 (CI95% 1-3)	**0,003**
Total tumor diameter at listing **Mean** ± SD (mm)	26	 52,4 ± 20,1	 25,3 ± 13,9	**0,002**
Unique tumor, ≤30 mm, n (%) No Yes	26 20 6	 18 (90%) 1 (16,7%)	 2 (10%) 5 (83,3%)	**0,0004**
AFP-level (UI/L) **at listing** **Mean** ± SD **Median** (CI 95%)	26	 8,8 ± 8,9 6 (CI95% 4-8)	 164,3 ± 213,1 42 (CI95% 2-513)	NS
AFP score at listing, n (%) 0 1 2 3	26 14 3 8 1	 10 (71,4%) 3 (100%) 6 (75%) 0	 4 (28,6%) 0 2 (25%) 1 (100%)	 NS

Milan criteria fulfilled at listing, n (%)	26			**0,039**
No	8	8 (100%)	0	
Yes	18	11 (61,1%)	7 (38,9%)	
Mean start dose ± SD (mg)	25	557,9 ± 216,8	800 ± 0	**0,018**
Dose increase, n (%)	25			**0,021**
No	15	9 (60%)	6 (40%)	
Yes	10	10 (100%)	0	
AFP score prior to LT, n (%)	26			**0,01**
≤ 2	24	19 (79,2%)	5 (20,9%)	
3	2	0	2 (100%)	
Last mRECIST radiological response prior to LT, n (%)				NS
CR	1	0	1 (100%)	
PR	6	6 (100%)	0	
SD	12	8 (66,7%)	4 (33,3%)	
PD	7	5 (71,4%)	2 (28,6%)	
Waiting time from listing to LT (months)	26			NS
Mean ± SD		13 ± 5,1	13,2 ± 2,8	
Median (CI 95%)		12,2 (CI 95% 11,2-13,9)	13,7 (CI 95% 10,1-16,8)	
Tumor number on explant, n (%)	25			NS
1	3	2 (66,7%)	1 (33,3%)	
2-3	3	2 (66,7%)	1 (33,3%)	
4-5	9	6 (66,7%)	3 (33,3%)	
≥6	10	8 (80%)	2 (20%)	
Extent of tumor necrosis, n (%)	16			NS
Complete (100%)	1	0	1 (100%)	
Subtotal necrosis (≥90%)	1	1 (100%)	0	
Partial necrosis (≥ 50% and <90%)	3	2 (66,7%)	1 (33,3%)	
Minimal necrosis (<50%)	9	6 (66,7%)	3 (33,3%)	
No necrosis (0%)	2	2 (100%)	0	

Differentiation grade, n (%)	25			NS
Well differentiated	16	13 (81,3%)	3 (18,8%)	
Moderately and poorly differentiated	8	5 (62,5%)	3 (37,5%)	
Not applicable (complete necrosis)	1	0	1 (100%)	
Satellite nodules, n (%)	17			0,06
No	13	6 (46,2%)	7 (53,8%)	
Yes	4	4 (100%)	0	
Microvascular invasion, n (%)				NS
No	21	16 (76,2%)	5 (23,8%)	
Yes	5	3 (60%)	2 (40%)	
Re-transplantation, n (%)	26			NS
No	25	19 (76%)	6 (24%)	
Yes	1	0	1 (100%)	

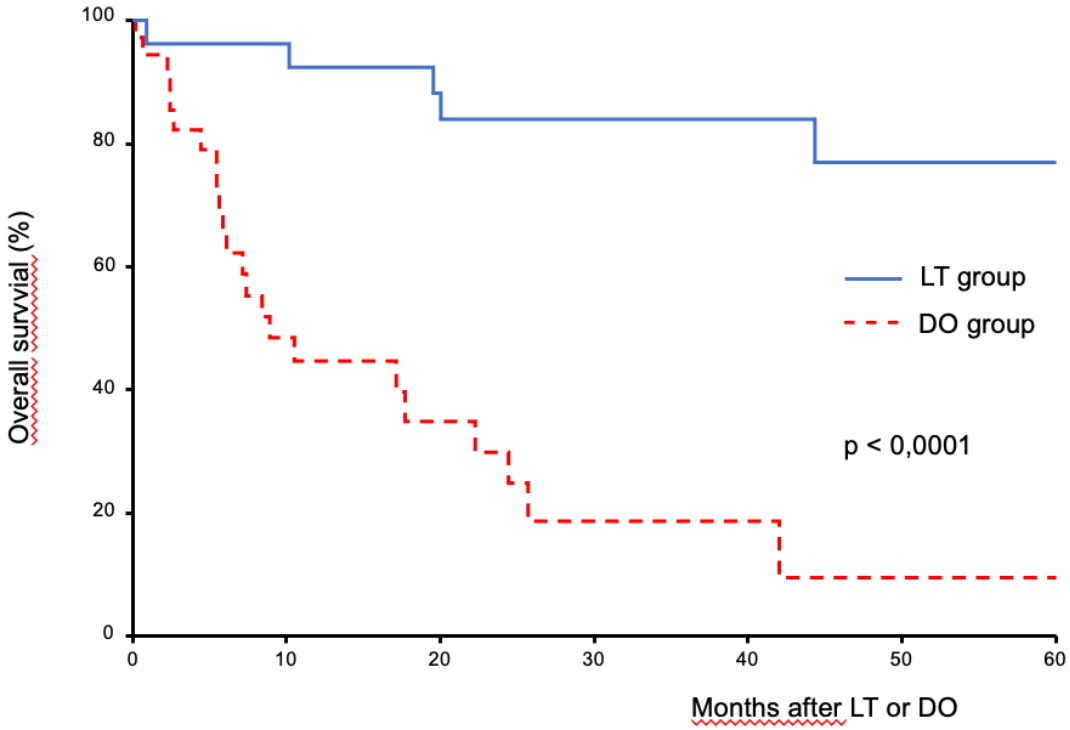
A logistic regression multivariate analysis was conducted to identify independent predictors of tumor recurrence after LT. We included in the logistic regression model the significant variables in univariate analysis. The model was adjusted for age. We had to remove the Milan criteria variable from the analysis because it was redundant with the AFP score prior to LT variable. Principal etiology of cirrhosis (non-alcohol related) (OR=0,1) and AFP score prior to LT (>2) (OR=0,0001) were independent predictors of tumor recurrence after LT. Results are outlined in table 8.

Table 8: Multivariate analysis of risk factors for HCC recurrence after LT

	Regression coefficient	**Odds ratio**	**95% confidence interval**	**p**
Age	0,05	1,05	(-144,97-145,07)	1
Alcohol as principal etiology of cirrhosis	**-2,3**	**0,1**	**(-4,25- -0,34)**	**0,02**
Tumor number at listing	-0,18	0,84	(-4,44-4,09)	0,93
Total tumor diameter at listing	-0,1	0,9	(-73,96-73,75)	1
Mean start dose	0,002	1	(-1859,09-1859,1)	1
Dose increase	0,5	1,66	(-0,45-1,46)	0,3
AFP score prior to LT	**7,51**	**1821,4**	**(7,13-7,89)**	**0,0001**

Mean and median follow-up time were 44,3±24 months and 44 months. The Kaplan-Meier survival curve is shown in figure 4. In the LT group, OS at years 1, 3 and 5 was 96,2%, 83,9% and 76,9%, respectively. In the DO group, OS at years 1, 3 and 5 was 48,4%, 18,6% and 0,09%, respectively. There was a significant difference in OS between the LT group and the DO group ($p<0,0001$).

Figure 4. Estimated overall survival after LT or after DO according to Kaplan-Meier



IV. Discussion

In the present study, we aimed to analyze natural history and trajectory of patients awaiting LT treated with So as 'neoadjuvant rescue therapy', peri-operative morbidity and overall and recurrence-free survival after LT. Principal results showed : 1) Twenty-six patients treated with So (42% of the cohort) underwent LT; 2) Peri-operative morbidity seemed not to be deeply impacted by use of So in a neoadjuvant setting, however a case control study may be useful to corroborate these results; 3) Independent factors predictive of HCC recurrence were principal etiology of cirrhosis (non-alcohol related) (OR=0,1) and AFP score prior to LT (>2) (OR=0,0001).

DO from the waiting list remains a major issue as 58% of our cohort experienced it for tumor progression. Among these patients, half dropped-out after around 8 months, exceeding the expected average DO rate of 20% at 12 months according to the Agence de Biomédecine data (4). In the literature, DO depends on multiple factors, including wait list time, tumor characteristics (solitary tumor greater than 3 cm, two or three tumor nodules), elevated baseline AFP level (≥100 ng/mL), increased AFP concentration, Child-Pugh status, MELD score at listing, use of bridge therapy and response to bridge therapy (21–25). Median waiting time of 12,5 months before LT in our study was consistent with the 12 months median waiting time according to the Agence de Biomédecine data (4). Our liver transplant candidates had compensated liver disease (median MELD 9), which is in line with the average score: approximately 75% of patients listed for HCC in 2019 had a MELD score < 15 (4). In our study, there was no significant difference in tumor burden, AFP level or MELD score at listing between the LT and the DO group which could explain an increase in the DO rate. Thus, other factors such as tumor biology, genetic signature and escape mechanisms may explain differences in terms of progression on the waiting list. Investigations of the mechanisms underlying the acquired resistance to So have been led in many studies. One of these mechanisms implicates overexpression of MET which leads to the activation of the Akt and ERK (extracellular signaling-regulated kinase) pathway (26).

So failed more frequently to prevent DO as compared with other studies in a neoadjuvant setting. Truesdale et al. reported that there were no DO for HCC progression among 10 patients in the So group of their study (14). Kulik et al. reported the occurrence of disease progression during the trial in only one patient under So and radioembolization and one patient of the control group (18). Frenette et al. recorded a 20% rate of DO for tumor progression in their study. One explanation for our higher

DO rate may lie in So treatment indication, which influenced significantly DO rate. Indeed, patients treated with So after tumor progression (50% of our cohort) had a significantly higher DO rate than patients treated with So because of impossibility of another loco-regional procedure (multifocal tumor or technical impossibility) (p=0,01). These findings corroborate those of Cuchetti et al. who showed that patients with no response to bridge therapy had the highest DO rates (24).

The most frequent treatment-related AEs related to So were dermatological disorders (41,9%), gastrointestinal disorders (37,1%) and fatigue (21%). These results are consistent with the most common events reported in major clinical trials (12,27). However, these events occurred less frequently in comparison to the safety reports from previous So monotherapy trials (16,17). Approximatively half of our cohort started So at full dose (400 mg twice daily) whereas in other neoadjuvant So studies, So was initiated at full dose in almost all patients. As a result, we reported fewer dose reductions in our study (41%) than in the other studies. In addition, mean So treatment time was 6 months, which is higher than findings in other neoadjuvant So studies where treatment duration ranged from 2,9 to 5,2 months (14–18).

In our cohort, the disease control rate (CR, PR and SD) was 73,2% in transplanted patients. Published series on mRECIST tumor response to TACE prior to LT showed similar rates ranging from 75% to 88% (28–30). Only one study assessed mRECIST tumor response to So, in combination with TACE (16). This study recorded a disease control rate of 69,5% prior to LT or drop-out.

One additional point of interest of our study is the well-known underestimation of tumor burden by radiological assessment, compared to histological findings, which is illustrated by the difference in sum of diameter between both evaluations. This notion

has been well described in the literature, with rates of tumor understaging by preoperative imaging ranging between 20% and 40% in most centers (29,31,32).

Interaction of So with the transplantation setting is of particular interest for transplant surgeons. High post-LT complication rates have been reported in patients receiving So before LT (14,18), but no firm conclusions can be drawn due to the small sample sizes, and other reports showed no increased complication rate (15–17). In our study, the incidence of bile duct stenosis was 11,5% and that of bile leakage was 3,8%. Kulik et al. and Truesdale et al. described both a potentially increased risk for biliary complications of respectively 62,5% and 67% in a So neoadjuvant setting (14,18). Our results were in parity with the estimated average rates of the systematic review conducted by Akamatsu in a total of 14359 liver transplantations, which were of 12% for biliary stricture and 7,8% for biliary leakage (33). Concerning thrombosis, incidence of hepatic artery thrombosis (HAT) was of 3,9% and of 1% for portal vein thrombosis in Duffy et al.'s cohort of 4234 LT recipients (34). In our study, we reported an unexpected higher rate of HAT of 11,5% and of portal vein thrombosis of 7,7%. Among all five (19%) patients who experienced HAT or portal vein thrombosis in our study, three (12%) patients had stopped So at least six months before LT, which makes the impact of So in the occurrence of thrombosis questionable. Finally, post-operative bleeding was observed in seven (27%) patients, of which four (15%) had continued So until LT and three (12%) had stopped treatment at least 2 months before LT. When considering only patients having continued So until LT, these results are below the 20% rate of bleeding leading to revision surgery reported by Schrem and al. (35). No pseudoaneurysm of the hepatic artery were noted in our study, whereas Eilard et al. and Truesdale et al. both recorded respectively a 16,7% and 11,1% rate of pseudoaneurysm of the hepatic artery. Thus, our study suggests that So use prior to

LT with discontinuation only on the day of transplantation appeared to be safe without increased risk of surgical or transplant-related complications. A case control study could be useful to accurately respond to the question of higher post-LT morbidity in transplanted patients treated with So.

The rationale for using So during waiting-list time relies in its potential to prevent recurrence. In France, use of AFP score identifies candidates with a 70% probability of recurrence-free survival at 5 years and allows LT for patients at low risk of recurrence without taking into account Milan criteria (36). Currently, we observe and consider as acceptable a recurrence rate < 15% 5 years following LT. Results of recurrence rates in previous neoadjuvant So studies were heterogenous, ranging from 0 to 42%, and impacted by limited sample size (14–18). In our cohort of 26 transplanted patients, seven patients (27%) experienced HCC recurrence, and 15 patients (58%) were alive and free of recurrence at the end of follow-up. Only two variables were identified as independent predictors of recurrence on multivariate analysis: principal etiology of cirrhosis (non-alcohol related) (OR=0,1) and AFP score prior to LT (>2) (OR=0,0001). This latter may be surprising as patients must be maintained in AFP score below 2 to access to LT. The explanation is that HCC burden had been retrospectively recorded as 3 instead of 2. The two patients with AFP score at 3 experienced HCC recurrence.

Observed five-year OS after LT was 77%, which is higher than the five-year OS rate of 72% reported by the Agence de la Biomédecine for patients having underwent LT in the HCC component, between 2007 and 2018 (4). However, recurrence free survival at around 50% is questionable in terms of ‘utility’ to transplant such patients,

even if new treatments have emerged and give huge benefit in terms of post-recurrence survival.

This study weakness is the nonrandomized design of the study. However, to our knowledge, this is the largest cohort reported to date of use of So in a neoadjuvant setting.

V. Conclusion

In conclusion, So as neoadjuvant rescue treatment provided access to LT for 42% of patients. Our analysis suggests the lack of huge ‘warning signal’ in patients treated with So when continued until the day of transplant. The 5-year recurrence free survival of 50% in our study was below the 70% 5-year recurrence free survival considered as the target standard of care. However, new targeted systemic therapies could improve the long-term outcome of LT recipients who experience recurrence.

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Date de soutenance : 14/09/2021
Titre de la thèse : Utilisation du sorafenib en situation néo-adjuvante pour carcinome hépatocellulaire en attente de transplantation hépatique.

Thèse - Médecine - Lille 2021
Cadre de classement : hépatologie, oncologie
DES + spécialité : DES d'hépato-gastroentérologie, FST de cancérologie
Mots-clés : Transplantation hépatique, Sorafenib, Carcinome hépatocellulaire

Résumé :
Contexte : Les données portant sur l'efficacité et la sécurité du Sorafenib (So) en situation néo-adjuvante pour CHC en attente de transplantation hépatique (TH) sont hétérogènes et rares. Notre étude avait pour objectif de décrire l'histoire naturelle des patients traités par So en attente de TH.
Patients et méthodes : Tous les patients inscrits sur liste entre mai 2010 et avril 2019 et traités par So en attente de TH ont été inclus. Une évaluation clinique et biologique était réalisée tous les mois. Une évaluation de la réponse radiologique tumorale selon mRECIST était entreprise de façon trimestrielle sur liste d'attente et semestrielle après TH.
Résultats : 327 patients ont été inscrits sur liste d'attente de TH pour CHC, parmi lesquels 62 (19%) étaient traités par So. Il s'agissait dans 82% des cas d'hommes âgés de 59 ans avec une cirrhose alcoolique dans 81% des cas. Le So était initié pour progression tumorale après traitement locorégional dans 50% des cas et pour impossibilité d'autres traitements dans 50% des cas. La durée moyenne de traitement était de 6 mois avec une posologie moyenne de 585 mg/jr. 36 (58%) patients sont sortis de liste pour progression tumorale et 26 (42%) patients ont été transplantés. Une réponse objective radiologique était obtenue chez 27% des patients transplantés versus 0% chez les patients sortis liste. Sept récidives (27%) ont été identifiées après un suivi moyen de 24 mois après TH. Les facteurs indépendants prédictifs de récidive étaient l'étiologie de la cirrhose et le dernier score AFP avant TH. La survie globale post-TH à 5 ans était de 77% et la survie sans récidive de 48%.
Conclusion : Le So a permis de maintenir un projet de TH pour 42% des patients considérés en impasse thérapeutique pour CHC. La survie sans récidive à 5 ans est inférieure à l'objectif actuel dans cette indication. Le dernier score AFP avant TH est un élément essentiel à prendre en considération.

Composition du Jury :

Président : Professeur Emmanuel BOLESLAWSKI
Assesseurs : Professeur Julien TAIEB, Docteur Charlotte VANVEUREN, Docteur Massih NINGARHARI
Directeur de thèse : Professeur Sébastien DHARANCY