Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

A prospective, randomized, multi-centre trial of systemic adjuvant chemotherapy versus no additional treatment in liver transplantation for hepatocellular carcinoma

Gunnar Söderdahl,[1] Lars Bäckman,[2] Helena Isoniemi,[3] Christian Cahlin,[2] Krister Höckerstedt,[3] Ulrika Broomé,[4] Heikki Mäkisalo,[3], Styrbjörn Friman[2] and Bo-Göran Ericzon[1]

1 Department of Transplantation Surgery, Karolinska University Hospital, Huddinge, Stockholm, Sweden
2 Department of Transplantation and Liver Surgery, Sahlgrenska University Hospital, Goteborg, Sweden
3 Department of Transplantation and Liver Surgery, University Hospital, Helsinki, Finland
4 Department of Gastroenterology and Hepatology, Karolinska University Hospital, Huddinge, Stockholm, Sweden

Keywords
chemotherapy, doxorubicin, hepatocellular carcinoma, liver transplantation.

Correspondence
Gunnar Söderdahl MD, Department of Transplantation Surgery, Karolinska University Hospital, Huddinge, SE-141 86 Stockholm, Sweden. Tel.: +46 8 58587621; fax: +46 8 7743191; e-mail: gunnar.soderdahl@karolinska.se

Received: 1 October 2005
Revision requested: 4 November 2005
Accepted: 9 January 2006

doi:10.1111/j.1432-2277.2006.00279.x

Summary

The role of adjuvant systemic chemotherapy in liver transplantation (LT) for hepatocellular carcinoma (HCC) is controversial. Here, we report the results of a Nordic prospective, randomized, multi-centre trial of systemic low-dose doxorubicin in patients with HCC. Between February 1996 and April 2004, 46 patients were randomized to receive either neoadjuvant doxorubicin in combination with LT (chemo group; $n = 19$) or LT alone (control group; $n = 27$). In the chemo group, doxorubicin was administered intravenously, 10 mg/m^2 weekly, starting from acceptance onto the waiting list for LT. One intraoperative dose of 15 mg/m^2 was given, and postoperatively doxorubicin was given weekly at a dose of 10 mg/m^2, depending on the clinical course, up to a cumulative dose of 400 mg/m^2. Actuarial, 3-year overall survival (OS) and disease-free survival (DFS) in the control group were 70% and 50%, respectively. In the chemo group, both OS and DFS were 63%. Freedom from recurrence at 3 years was 55% in the control group and 74% in the chemo group. None of the differences was statistically significant. Neoadjuvant treatment with systemic low-dose doxorubicin seems not to improve either survival or freedom from recurrence in patients with HCC undergoing LT.

Introduction

Liver transplantation (LT) in unselected patients with hepatocellular carcinoma (HCC) has an inferior prognosis compared with other established indications, mainly because of a high recurrence rate [1,2]. The rate of recurrence is strongly correlated to the size of the tumour and to the number of tumour nodules [3], parameters that may serve as surrogate markers for vascular invasion and potential metastatic capacity [4]. Because of the scarcity of available donor grafts, most centres have been forced to adopt strict selection criteria for LT in patients with HCC. Currently, the Milan criteria are universally accepted, which means that only patients with a single tumour no more than 5 cm in size or with tumours consisting of fewer than four nodules, individually no more than 3 cm in size, can be candidates for LT [5]. When these criteria are applied, the recurrence rate is low and recurrences are mainly seen in those patients in whom preoperative imaging has failed to stage the tumour correctly [6]. The treatment protocol for patients not meeting the Milan criteria is not well established. Trials of systemic chemotherapy have failed to show any survival benefit, although partial tumour response is sometimes seen. In patients with an 'intermediate'-staged tumour, tumour-selective, intra-arterial chemotherapy with or without embolization has been shown to increase medium-term survival in two randomized-controlled studies [7,8]. However, the

survival benefit is low, and long-term data are not yet available. For patients with advanced tumours, although radiologically restricted to the liver, only palliative treatment can be advocated.

The rationale for adjuvant systemic chemotherapy is to limit the growth of already established microscopic spreading of the tumour outside the liver at the time of LT. Adding chemotherapy before LT as well, either systemically or intra-arterially or both, may also reduce the risk that tumour cells might seed into the circulation through manipulation of the liver during surgery. Thus, by decreasing tumour cell viability before transplantation, the risk of recurrent tumour establishment may theoretically decrease.

Several pilot trials of adjuvant or neoadjuvant systemic chemotherapy in LT for patients with HCC have been performed over recent decades. One of the first, which suggested a beneficial effect from low-dose, weekly administered, neoadjuvant doxorubicins was first reported by Stone *et al.* [9] in 1991 and then later in 1993. That particular study found that the 3-year survival of treated patients increased from 20% to 50% compared with historical controls. Since then, a number of similar small, uncontrolled studies with different protocols have been carried out, some finding a positive effect from adjuvant treatment, some not [10–12]. A recent controlled study of i.v. neoadjuvant doxorubicin given bi-weekly observed no effect on either survival or disease-free survival (DFS) [13].

In the present prospective, randomized, multi-centre study of patients with HCC restricted to the liver but not meeting other tumour selection criteria, we have investigated the effect of weekly systemic neoadjuvant, low-dose, doxorubicin in combination with LT in comparison with LT without additive treatment.

Materials and methods

Study design

Between February 1996 and April 2004, adult patients with unresectable HCC, referred for LT in three different Scandinavian centres, were randomized to receive either neoadjuvant chemotherapy plus LT (chemo group) or LT alone (control group). In the chemo group, patients received i.v. doxorubicin, 10 mg/m^2 weekly, starting from acceptance onto the waiting list. Intraoperatively, one 15-mg/m^2 dose of doxorubicin was given, and the treatment continued postoperatively in the same manner as preoperatively until a total dose of 400 mg/m^2 had been achieved. Pre- or perioperative evidence of extrahepatic spread was an exclusion criteria, otherwise there were no selection criteria regarding tumour size, number of nodules, or intrahepatic vascular invasion. There could be no history of advanced cardiac disease and the left ventricular ejection fraction as judged by echocardiography had to be normal. Patients with tumours not previously known before LT (incidental) were allowed to be randomized during the first 2 weeks postoperatively. The study was originally designed for 90 patients with an interim analysis to be conducted when 45 patients had been randomized. After interim analysis, however, it was decided to stop further inclusions in the study because of low probability for obtaining difference in outcome parameters between the groups. Block randomization was employed for each centre. Outcome parameters were 3-year overall survival (OS), 3-year DFS, and 3-year freedom from recurrence. All patients were followed after LT using computed tomography (CT) of the abdomen and chest X ray every 12 months. In addition, alpha-fetoprotein (AFP) was measured every 3 months for the first year and every 6 months thereafter. Informed consent was obtained from all patients, and all procedures performed were in accordance with the ethical standards of the institutional board of each participating centre.

Patient and donor characteristics (Table 1)

A total of 46 patients were randomized during the study period. Of these, four were withdrawn from the study because of either wrong diagnosis ($n = 2$) or evidence of extrahepatic growth at the time of transplantation ($n = 2$). Of the 42 remaining patients, 17 were randomized to the

Table 1. Patient characteristics and postoperative parameters.

	Chemo group	Control group	*P*
Number of randomized patients	19	27	–
Number of evaluated patients	17	25	–
Patient age (mean ± SD)	55.4 ± 9.1	57.7 ± 8.6	0.536
Sex proportion (M/F)	82.4/17.6	84/16	1.000
Waiting time, days (mean ± SD)	29.6 (26.1)	43.3 (42.1)	0.206
Positive hepatitis B serology, prop.	6.2	12.0	0.545
Positive hepatitis C serology, prop.	31.2	36.0	0.754
Immunosuppression, prop. (CyA/Tac)	47.3/52.7	58.3/41.7	0.537
Rejection episode, prop. (Yes/no)	68.7/31.3	41.7/58.3	0.117
Bilirubin , postop. day 30 (μmol/l, mean ± SD)	48.7 ± 85.6	41.4 ± 62.7	0.765

Prop = proportion; CyA = cyklosporin A; Tac = tacrolimus.

chemo group while 25 were randomized to the control group. The difference in number of patients between the two groups could only be explained by chance and the random selection among the prescheduled 45 cases in each group. Forty donors were cadaveric while two were live, whole-liver donors with a diagnosis of familial amyloidotic polyneuropathy, undergoing LT with a graft from a cadaveric donor at the same time (domino transplantation).

Tumour characteristics (Table 2)

Staging of the tumour was performed both preoperatively using ultrasonography and CT, and postoperatively by means of histological analyses of the explant. When not otherwise stated, measurements and other staging parameters referred to were registered during post-transplant examination. We deliberately choose not to exclude tumours outside the Milan criteria in order to have a reasonable chance to detect statistical differences between the two groups and to make this trial comparable with a previous reported nonrandomized pilot trial with neo-adjuvant adriamycin [9]. The tumours in the control group differed somewhat from those in the chemo group, in that there was a higher proportion of tumours with greater than two nodules and a lower proportion of tumours with high differentiation. Consequently, the proportion of tumours that met the Milan criteria (classified from preoperative imaging) was somewhat higher in the chemo group, although not statistically significantly so.

Immunosuppressive regimen

The immunosuppressive regimen was not defined other than that azathioprine should be avoided in both groups. Otherwise, the current immunosuppressive protocol of each centre was followed. There was no difference in the use of monoclonal antibodies for induction or rejection treatment between the two groups.

Statistical analysis

This study was designed to detect a difference in 3-year patient survival of 30% (from 25% to 55%) between the groups with a power of 80% at a significance level of 5%. Differences in proportion between groups were analysed with Fischer's exact test or the chi-squared test. Differences in means between groups were tested with Student's *t*-statistic. Survival analyses were performed using the Kaplan–Meyer product limit method for comparing multiple samples. Regression analyses were performed using the proportional hazard (Cox) method for single or multiple variates.

Results

Adherence to study protocol and side effects

In the chemo group, 10 of the 17 patients underwent the scheduled number of treatments, achieving a cumulative doxorubicin dose of 400 mg/m^2, while six patients received total doses of <200 mg/m^2. In the majority of cases, interruption or permanent withdrawal of chemotherapy was because of poor general condition and/or signs of liver failure. There was no case for a strong casual relationship between the doxorubicin treatment and the poor performance seen, but as a relationship not could be excluded, most of these patients were not reinstated into the treatment. Side effects were otherwise not pronounced, and among patients who tolerated chemotherapy during the first 3 months, only one of the 11 stopped therapy prematurely.

Table 2. Tumour characteristics.

	Chemo group $n = 17$	Control group $n = 25$	Chi-square/*t*	*P*-value
Size class < 5 cm	23.5%	32.0%	0.4	0.550
Size class 5–10 cm	47.0%	44.0%	0.1	0.845
Size class > 10 cm	29.4%	24.0%	0.2	0.695
Number of foci > 2	25.0%	44.0%	1.5	0.218
Histological grade, medium or low differentiated tumours	35.7%	71.4%	4.4	0.036
Milan criteria fulfilled	47.1%	32.0%	1.0	0.324
Cirrhosis	76.5%	92.0%	2.0	0.158
Vascular invasion	33.3%	29.2%	0.1	0.784
Capsule invasion	20.0%	8.3%	1.1	0.289
Size of largest nodule, mean, cm (SD)	5.65 (3.81)	4.80 (2.37)	$t = 0.87$	0.389
10 log alpha-fetoprotein (AFP) in serum, mean (SD)	1.69 (1.00)	2.03 (1.20)	$t = 0.92$	0.364

Size class = summarized total tumour diameter.

Survival

Actuarial 3-year survival was 70% in the control group and 63% in the chemo group ($P = 0.968$). When 5-year survival was calculated, it was 58% in the control group and 63% in the chemo group (Fig. 1). In the subgroup of patients who met the Milan criteria, 5-year survival was 83% in the control group and 73% in the chemo group ($P = 0.303$), whereas in patients not meeting the criteria, 5-year survival was 33% and 55%, respectively ($P = 0.748$).

Disease-free survival (DFS)

The 3-year DFS was 50% in the control group and 63% in the chemo group ($P = 0.294$) (Fig. 2). There was a trend towards an increased percentual difference between the groups if the analysis was performed on the subgroup of patients that did not meet the Milan criteria and when the analysis was prolonged to 5 years (12% vs. 55%). However, this trend was counteracted by the diminished statistical power of the analysis, so the difference was not statistically significant ($P = 0.303$).

Freedom from recurrence

Calculation of the proportion of patients free from recurrence after 3 years was performed using the Kaplan–Meyer method for comparing two samples. Only recurrence was regarded as an event, and patients who died of causes other than recurrence were censored, as patients were without recurrence and still alive at the time of follow-up. The cumulative proportion of patients free from recurrence at 3 years was 55% in the control group and 73% in the chemo group ($P = 0.265$) (Fig. 3), while among patients not meeting the Milan criteria, the proportion was 43% and 56%, respectively ($P = 0.698$).

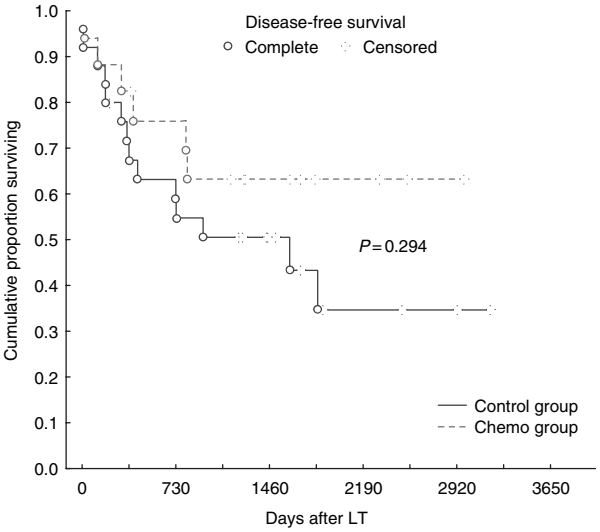

Figure 2 Kaplan–Meier graph showing disease-free survival in the control group ($n = 25$) versus the chemo group ($n = 17$). Recurrence or death is recorded as events, and patients without recurrence at follow-up are censored.

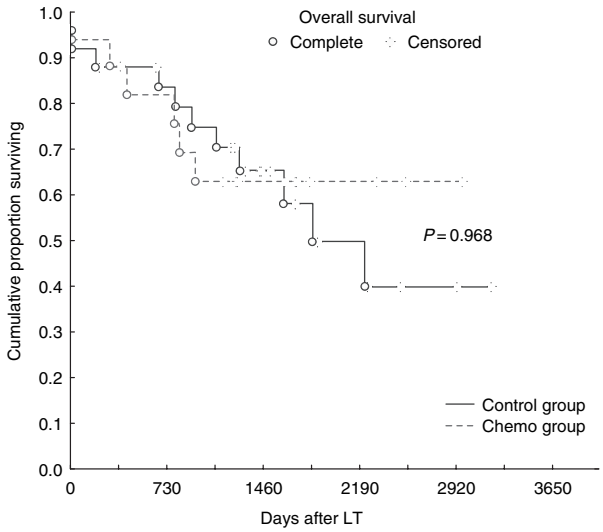

Figure 1 Kaplan–Meier graph showing overall patient survival in the control group ($n = 25$) versus the chemo group ($n = 17$). Death is recorded as an event, and patients who are still alive at follow-up are censored.

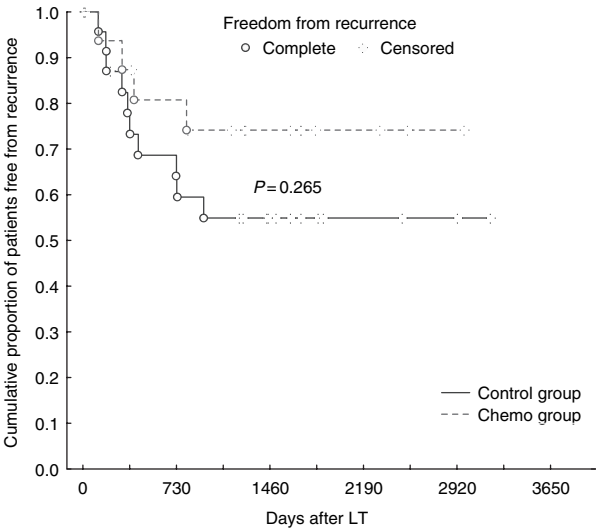

Figure 3 Kaplan–Meier graph showing freedom from recurrence in the control group ($n = 25$) versus the chemo group ($n = 17$). Recurrence is recorded as an event, and patients who died for other reasons or did not develop recurrence by follow-up are censored.

Risk factors for decreased survival

Cox regression analysis of factors that might determine survival was performed, adjusting for the difference between the groups in the proportions of patients who did and did not meet the Milan criteria. Only total tumour size and size of the largest nodule were found to be significant factors affecting the survival (Table 3). In the stepwise regression analysis, when size of the largest nodule was taken into consideration, no other factor could significantly explain the variation in survival. Treatment with neoadjuvant doxorubicin did not have any influence on survival.

Risk factors for recurrence

When analysing for factors that might determine recurrence, total tumour size, size of largest nodule, and number of nodules all achieved statistical significance in the adjusted univariate analysis (Table 4). In the stepwise regression analysis, when total tumour size was taken into consideration, no other factor could further explain the difference in freedom from recurrence. Again, neoadjuvant treatment with doxorubicin did not significantly affect the recurrence rate. However, when excluding patients in the chemo group who received fewer than half the number of scheduled treatments, a significantly greater proportion of patients were free from recurrence in the chemo group than in the control group ($P = 0.022$).

Discussion

Management of patients with HCC is frustrating, because only a minority of cases are amenable to potential curative surgical modalities such as liver resection or LT. In patients with liver cirrhosis, LT has the theoretical advantage of radical tumour removal, elimination of neocarcinogenesis in the remaining liver, and the potential to cure the patient from the underlying liver disease. Although the recurrence rate after LT in cirrhosis is probably lower than after liver resection for a given tumour, it is not negligible, and thus survival is inferior compared with other established indications. Only patients with very early tumours are therefore considered for LT, leaving the vast majority of patients without any chance of curative treatment.

Adjuvant or neoadjuvant treatment in conjunction with LT is theoretically attractive, as the remaining tumour burden is generally low. As tumour cells may escape the liver before the time of transplantation, systemic treatment should ideally be part of such a protocol. Hepatocellular carcinoma generally responds poorly to chemotherapy, demonstrating extensive multi-drug resistance [14]. Nevertheless, doxorubicin, the single most effective drug for established HCC, can give an objective

Table 3. Cox regression analysis with respect to survival. All patients.

					95.0% CI for RH		
	Wald	d.f.	*P*	RH	Lower	Upper	*P* (adj.)
Doxorubicin	0.11	1	0.742	0.85	0.31	2.19	0.836
Size class > 10 cm	6.08	1	0.014	3.42	1.29	9.08	
Size of largest nodule	9.17	1	0.002	1.25	1.08	1.45	
Milan criteria fulfilled	3.39	1	0.066	0.31	0.09	1.08	
Age	0.10	1	0.757	0.99	0.93	1.06	
Cirrhosis	0.02	1	0.885	0.91	0.26	3.18	
Vascular invasion	0.55	1	0.459	1.47	0.53	4.07	
Capsule invasion	0.43	1	0.514	1.53	0.43	5.45	
Time on waiting list	2.11	1	0.146	0.98	0.96	1.01	
Number of nodules > 2	0.88	1	0.349	1.62	0.59	4.40	
Histological grade medium or low diff.	1.77	1	0.184	2.23	0.68	7.28	
Log AFP	0.73	1	0.392	1.20	0.79	1.81	

P (adj) = *P*-value adjusted for the difference in proportion of patients between the groups that fulfilled the Milan criteria.
Size class = summarized total tumour diameter.
Diff. = tumour differentiation
RH = relative hazard.
Wald = test statistic.

Table 4. Cox regression analysis with respect to recurrence. All patients.

					95.0% CI for RH		
	Wald	d.f.	*P*	RH	Lower	Upper	*P* (adj.)
Doxorubicin	0.88	1	0.350	0.57	0.18	1.85	0.429
Size class > 10 cm	10.7	1	0.001	6.74	2.14	21.2	
Size of largest nodule	8.24	1	0.004	1.26	1.08	1.47	
Milan criteria fulfilled	3.50	1	0.061	0.24	0.05	1.07	
Age	0.01	1	0.913	1.00	0.93	1.07	
Cirrhosis	0.58	1	0.445	0.60	0.17	2.20	
Vascular invasion	0.42	1	0.519	1.45	0.47	4.42	
Capsule invasion	1.86	1	0.172	2.47	0.68	9.00	
Nodules > 2	4.13	1	0.042	3.20	1.04	9.81	
Time on waiting list	1.87	1	0.171	0.98	0.96	1.01	
Histological grade, medium or low diff.	0.60	1	0.437	1.65	0.47	5.87	
Log AFP	0.28	1	0.594	1.14	0.71	1.81	

P (adj) = *P*-value adjusted for the difference in proportion of patients between the groups that fulfilled the Milan criteria.
Size class = summarized total tumour diameter.
Diff. = tumour differentiation.
RH = relative hazard.
Wald = test statistic.

response rate in 15–20% of cases [15] and was therefore chosen as neoadjuvant additive in this trial.

The trial was initially designed for 90 patients; however, at the interim analysis, it was judged that a significant difference between the two groups was unlikely to occur and the trial was stopped prematurely. When analysing the results of the 46 randomized patients, it was clear that there was no trend towards survival benefit at 3 years in either of the groups. When analysing the endpoint of freedom from recurrence at 3 years, there was a slight trend towards fewer recurrences in the chemo group; however, the tumours in that group were somewhat less advanced at the outset of the study than were those in the control group (Table 2), which could very well explain the difference. The only significant difference noted was when analysis of the chemo group was restricted to patients who received more than half of the scheduled doxorubicin treatments. When this sub-group was compared with the control group, treatment with doxorubicin was found to be associated with a lower rate of recurrence, even when the analysis was adjusted for the difference in proportion of advanced tumours between the groups. On an intention-to-treat basis, however, this difference is of limited value and highlights one of the difficulties with chemotherapy after LT, namely, poor tolerability.

Our results support a recently published trial in which a similar protocol was applied in a cohort of patients with almost the same tumour characteristics as those in the present trial [13]. In contrast to our study, doxorubicin (15 mg/m^2) was given biweekly up to a total of 20 cycles with a cumulative dose 300 mg/m^2, while in the present study patients were scheduled for 40 weekly doses (10 mg/m^2), leading to a cumulative dose of 400 mg/m^2. It is therefore unlikely that the negative results of adjuvant low-dose doxorubicin found in that particular study were because of too infrequent dosing or to a suboptimal cumulative dose of doxorubicin. On the other hand, as only 59% of the patients in our study could tolerate all the prescheduled number of doses, a further intensified regime seems impractical. Whether a high-dose protocol with doses every third or fourth week would be better was not investigated; but again, the risk of hepatotoxicity in this subset of patients is the limiting factor that determines what can be administered in a neoadjuvant or adjuvant setting.

It has recently been found that experimentally induced liver tumours may respond differently to doxorubicin, especially when treatment is administered in combination with cyclosporin A [16]. In that study, tumours with severe dysplasia were growth-inhibited by doxorubicin, but the inhibition was partly counteracted by the addition of cyclosporin A. Tumours with low-grade dysplasia were found to be paradoxically growth-stimulated by the combination of doxorubicin and cyclosporin A, compared with tumours in untreated control animals. The reason for this stimulatory effect is unclear, but well-differentiated tumour cells that are resistant to doxorubicin may have retained their capacity to respond to growth factors induced by the treatment effect on surrounding normal hepatocytes. If this is also true in the human setting, the lack of positive response to neoadjuvant doxorubicin

treatment in terms of the tumour recurrence rate after LT in patients with unselected tumours is not surprising.

It cannot be ruled out, however, that there may be a heterogenous responsiveness, and that some patients would actually benefit from the treatment. This study was not designed to identify such differences, so thus far, we have no tools for predicting which patients should possibly receive this kind of treatment. Further studies focusing on differential treatment protocols based on the pretransplant morphology/cytogenetics may therefore be of interest.

We conclude that, on an intention-to-treat basis, neoadjuvant treatment with low-dose systemically administered doxorubicin in LT for HCC is of no benefit with regards OS, DFS, or freedom from recurrence. The possible positive effect on freedom from recurrence of doxorubicin treatment in patients who manage to complete the protocol is counteracted by an increased nonrecurrence-related mortality rate in this group. Together with previously reported data derived from a similar, but less intensive protocol, this study strongly indicates that neoadjuvant doxorubicin treatment is not useful for improving survival in HCC patients after LT.

Acknowledgements

The authors wish to thank Bo Nilsson for providing statistical assistance in the preparation of this manuscript.

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