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Treatment of adult acute lymphoblastic leukaemia using an intensive chemotherapy protocol

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Summary. A total of 25 evaluable adult patients with acute lymphoblastic leukaemia (ALL) were treated with an intensive chemotherapy regime modified from the L17/L17M protocol of the Sloan-Kettering Hospital. There were 18 men and 7 women; their median age was 36 years (range, 13–78). Seven cases had L1 morphology and 18, L2. The immunophenotype was common-ALL in 10, null-ALL in 9, T-ALL in 4 and B-ALL in 1. Of the 25 patients, 14 (56%) achieved a complete remission (CR). The causes of induction failure were partial remission (PR) only in 7 (28%) and hypoplastic death in 4 (16%). Of the 14 CR patients, 11 (78.6%) relapsed. Five patients developed CNS disease. The median disease-free survival and overall survival were only 9 and 13 months, respectively. As the follow-up periods of the surviving patients were short, late relapses may still occur and the overall treatment result is likely to be worse on longer follow-up. The possible causes of this disappointing result are discussed.

Introduction

Acute lymphoblastic leukaemia (ALL) accounts for almost 90% of acute leukaemias in young children. With effective treatment regimens, over 90% of these children achieve complete remissions (CRs) and half of them are cured [13, 19]. ALL is less common in adults and comprises only 20% of the acute leukaemia in patients above the age of 15 [8, 10, 13]. Treatment results in adult ALL have thus far been disappointing, but in recent years improved results have been achieved in adult ALL treated with intensive chemotherapy protocols [1, 4, 5, 7, 11, 14, 15]. The L10/L10M and L17/L17M protocols in the experienced hands of the Sloan-Kettering group have achieved remarkable treatment results [4]. We present the results of a regime, modified from the L17/L17M protocol, in our previously untreated adult patients with ALL.

Patients and methods

Patients aged >12 years with previously untreated ALL who were seen in the Department of Medicine, University of Hong Kong, Queen Mary Hospital entered this study between October 1984 and December 1987. Pretreatment assessments included: history and physical examination, blood biochemistry, peripheral blood and bone-marrow smear examination, coagulation tests (prothrombin time, activated partial thromboplastin time and fibrinogen level), antibody to HTLV-I virus and chest radiograph.

Cases were classified morphologically according to the FAB system [3]. Cytochemical stainings for Sudan black, PAS, chloroacetate esterase, non-specific esterase and acid phosphatase were carried out. Myeloperoxidase staining was used when the result of Sudan black staining was equivocal. The immunophenotype was determined by the immunoperoxidase technique, using a panel of commercially available monoclonal antibodies [9]. Chromosomal analysis was done only when chronic myeloid leukaemia was suspected due to massive splenomegaly, the presence of immature white cells of intermediate forms in the peripheral blood, a normal platelet count or the anomalous expression of myeloid markers [2, 18].

Patients were diagnosed as having ALL if they showed compatible morphology, negative staining for Sudan black B or myeloperoxidase, and compatible immunophenotypes. CNS disease was diagnosed by the detection of lymphoblasts in CSF. Patients were excluded due to prior therapy or the presence of the Philadelphia chromosome.

Patients were hydrated and put on 300 mg allopurinol daily before the start of chemotherapy. Induction chemotherapy was begun according to a protocol that was modified from the L17/L17M protocols of the Sloan-Kettering group (Table 1). Patients with bulky enlargement of the lymph nodes, liver or spleen were given an additional dose of cyclophosphamide on day 0. Repeated marrow aspirate examinations were carried out on days 14, 21 and 28 to assess response. Standard criteria of responses and failures were used [20]. Patients not achieving CR after day 28 were given a second-line induction regime consisting of methotrexate, vincristine, L-asparaginase and dexamethasone [6]. Those achieving CR went on to the consolidation and maintenance therapy (Table 1). Prophylactic cranial irradiation was given immediately following consolidation therapy.

During the induction therapy, patients received prophylactic cotrimoxazole or ofloxacin. Episodes of fever and neutropaenia were treated with i.v. broad-spectrum antibiotics. Platelet transfusions were given prophylactically to maintain the platelet count at $>10\times10^9$/l, and red cell transfusions were given according to standard

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transfusion practice. Leucocyte transfusions were not routinely used.

The CR and relapse rates were expressed with a confidence interval (CI) [17]. The Kaplan-Meier product-limit method was used to generate disease-free survival (DFS) and overall survival curves [12]. DFS time was measured from the date of first remission to the date of first relapse, and the overall survival time was measured from the date of first diagnosis to the date of death or last follow-up. The log-rank procedure was used to compare survival curves, and the chi-square test with Yates' correction was used to compare CR and relapse rates.

Table 1. The protocol for treatment of ALL

(I)	Induction	
	Vincristine	1.4 mg/m² (maximum, 2 mg) i.v., days 0, 7, 14, 21, 28
	Cyclophosphamide	600 mg/m² i.v., day 0 (patient with bulky disease)
	Doxorubicin	20 mg/m² i.v., days 16, 17, 18
	Prednisone	60 mg/m² p.o. daily, days 0–28, then tapering over 7 days
	Cyclophosphamide	600 mg/m² i.v., day 34
	Doxorubicin	30 mg/m² i.v., day 34
	Methotrexate	6 mg/m² (maximum, 10 mg) intrathecally, days 13, 15, 31, 33 (if platelet count is $> 50 \times 10^9$/l and no blasts are observed in peripheral blood)
(II)	Consolidation	
(A)	Daunorubicin	60 mg/m² i.v., days 1 and 2
	Ara C	100 mg/m², 18-h i.v. infusion daily, days 1–5
	Methotrexate	6 mg/m² (maximum, 10 mg) intrathecally, days 1 and 3
	Rest 21–28 days	
(B)	Ara C	100 mg/m², 18-h i.v. infusion daily, days 1–4
	Methotrexate	15 mg/m² i.v., days 1–4
	Methotrexate	6 mg/m² (maximum, 10 mg) intrathecally, day 1
(C)	L-asparaginase	20,000 IU/m² i.v., 3 times per week for 6 doses
(D)	Cyclophosphamide	1200 mg/m² i.v., 1 dose
(III)	Cranial irradiation: 2,000 cGy in 10 fractions Local radiotherapy for bulky disease (optional)	
(IV)	Maintenance	
(A)	Sequence I:	
	Vincristine	1.4 mg/m² (maximum, 2 mg) i.v., days 0 and 7
	Prednisone	60 mg/m² p.o. daily, days 1–7
	Doxorubicin	20 mg/m² i.v., days 14–16
	Rest 2 weeks	
	6-mercaptopurine	90 mg/m² p.o. daily, days 1–28
	Methotrexate	20 mg/m² p.o. weekly, days 7, 14, 21, 28
	Methotrexate	6 mg/m² (maximum, 10 mg) intrathecally, days 1 and 3
	Rest 1 week	
	Dactinomycin	1 mg i.v., 1 dose
(B)	Sequence II:	
	Same as sequence I, except instead of doxorubicin on days 14–16:	
	CCNU	40 mg p.o., 1 dose, day 14
	Cyclophosphamide	800 mg/m² i.v., 1 dose, day 14
	Sequences I and II were given successively for 3 years	
	Intrathecal methotrexate was omitted after 2 years	

Results

A total of 30 consecutive patients entered the study; the clinical characteristics of the 25 evaluable patients are shown in Table 2. The other five patients were excluded due to prior chemotherapy in two, presence of the Philadelphia chromosome in two and violation of protocol in one. None of the patients were excluded because of their clinical condition.

The 25 evaluable patients presented with bleeding (56%), anaemia (32%), fever (28%), cough (24%), weight loss (12%), dyspnoea (12%), oral ulcers (4%), bone pain (4%) and abdominal pain (4%). Of these patients, 14 (56%; 95% CI, 37.1%–73.3%) achieved CRs. The causes of the 11 induction failures were partial remissions (PRs) only in 7 (28%) and hypoplastic deaths in 4 (16%). Of the 14 CR patients, 11 relapsed (78.6%; 95% CI, 52.5%–92.4%); only 3 remained in CR 8+, 26+ and 32+ months. Of the 11 relapses, 6 occurred at the time of consolidation therapy and the remaining 5, at maintenance. The disease-free survival of CR patients and the overall survival of all patients are shown in Figs. 1 and 2, respectively.

Table 2. Patient characteristics

		Number of patients (%)
Total number of patients		25 (100%)
Sex:	male	18 (72%)
	female	7 (28%)
Age (years):	median	36
	range	13–78
Morphology:	L1	7 (28%)
	L2	18 (72%)
	L3	0 (0%)
Immunophenotype:		
common ALL[a]		10 (40%)
null-ALL[a]		9 (36%)
T-ALL[b]		4 (16%)
B-ALL		1 (4%)
unknown		1 (4%)
Organomegaly:		14 (56%)
lymph nodes		7 (28%)
liver		12 (48%)
spleen		12 (48%)
White cell count ($\times 10^9$/l):		
mean		110
median		19
range		1.2–567
Platelet count ($\times 10^9$/l):		
mean		59
median		38
range		3–257
HTLV-I Ab		0

[a] My 7 was positive in 1 patient
[b] Became null-ALL at relapse in 1 patient

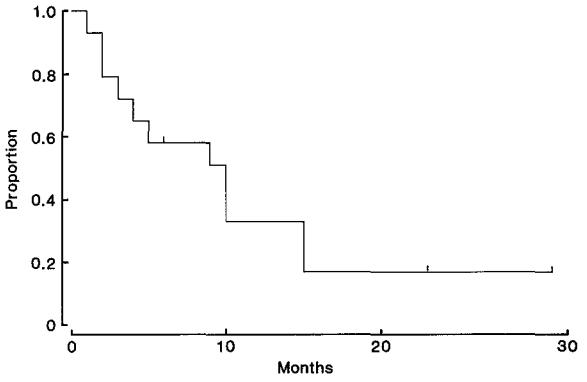

Fig. 1. The disease-free survival of 14 CR patients with ALL

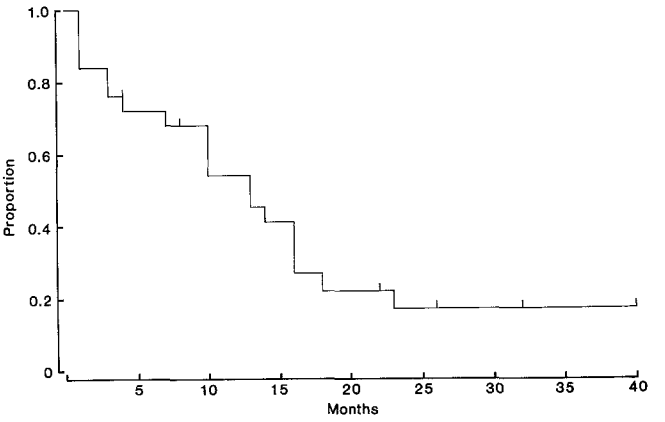

Fig. 2. The overall survival of all 25 patients with ALL

Four of the seven PR patients (57.1%) achieved CR (lasting for 1+, 7, 18+ and 36 months) following second-line induction chemotherapy using methotrexate, vincristine, L-asparaginase and dexamethasone. The patient whose CR lasted for 18+ months had an allogeneic bone marrow transplantation. However, the same second-line regime failed to induce remission when it was used in nine CR patients at their first relapse.

Five patients, including two men and three women, developed CNS disease; their ages were 13, 14, 26, 36 and 57 years. Four of them had L2 disease and the remaining one, L1; two had common-ALL and three null-ALL. Organomegaly occurred in two patients. The white cell counts of these five patients at the time of initial diagnosis were 4.8, 33, 263, 358 and 567 $\times 10^9$/l. Four of these patients had achieved CRs lasting 3, 5, 13 and 15 months prior to the development of CNS disease, which occurred at the time of consolidation therapy in three patients and maintenance therapy in two. The intervals between the initial diagnosis and CNS disease were 4, 5, 9, 10 and 12 months. All five patients had prophylactic intrathecal methotrexate therapy, but only two had received prophylactic cranial ir-

Table 3. Effect of prognostic variables on results of therapy

	CR rate	Relapse rate	DFS of CR patients		Overall survival of all patients		
			at 12 months	median	at 1 year	at 2 years	median
All patients	14/25 (56%)	11/14 (78.6%)	33%	9 months	54%	17%	13 months
Sex: male	9/18 (50%)	8/9 (88.7%)	14%	9 months	46%	13%	10 months
female	5/7 (71.4%)	3/5 (60%)	60%	15 months	71%	27%	18 months
Age (years): <40	10/15 (66.7%)	8/10 (80%)	25%	7.5 months	63%	12%	14 months
>40	4/10 (40%)	3/4 (75%)	50%	12.5 months	40%	20%	3 months
FAB: L1	3/7 (42.9%)	3/3 (100%)	0	5 months	52%	not reached	13 months
L2	11/18 (61.1%)	8/11 (72.7%)	42%	10 months	55%	19%	13 months
Phenotype:							
common-ALL[a]	6/10 (60%)	5/6 (83.3%)	44%	10 months	70%	not reached	14 months
null-ALL[a]	5/9 (55.6%)	4/5 (80%)	20%	9 months	44%	22%	10 months
T-ALL[b]	2/4 (50%)	1/2 (50%)	–	–	–	–	–
B-ALL	1/1 (100%)	1/1 (100%)	–	–	–	–	–
unknown	0/1 (0)	–	–	–	–	–	–
Organomegaly:							
Yes	9/14 (64.3%)	7/9 (77.8%)	27%	9 months	53%	17%	14 months
No	5/11 (45.5%)	4/5 (80%)	40%	9 months	55%	19%	13 months
Initial white cell count							
($\times 10^9$/l): 4–50	9/14 (64.3%)	6/9 (66.7%)	40%	9 months	52%	35%	16 months
<4	1/4 (25%)	1/1 (100%)	20%	3 months	46%	0	10 months
>50	4/7 (57%)	4/4 (100%)					
Initial platelet count							
($\times 10^9$/l): <50	9/15 (60%)	8/9 (89%)	23%	5 months	52%	15%	13 months
>50	5/10 (50%)	3/5 (60%)	54%	15 months	58%	23%	16 months
CNS disease (any time):							
Yes	4/5 (80%)	4/4 (100%)	5%	7.5 months	60%	0	13 months
No	10/20 (50%)	7/10 (70%)	36%	9 months	53%	23%	13 months

[a] Anomalous expression of My 7 in 1 patient
[b] Became null-ALL at relapse in 1 patient

radiation prior to the development of CNS disease. Two patients had simultaneous systemic disease at the time of CNS relapse. For the other three patients, systemic relapse occurred at 1, 4 and 13 months following CNS relapse. CNS disease was treated with intrathecal methotrexate and/or ara C. Cranial irradiation was given if it had not previously been received. Control of CNS disease was achieved in all patients, but they all died of uncontrolled systemic leukaemia.

Factors that might have influenced the treatment results were analysed and are summarised in Table 3. However, because of the small number of patients in the subgroups, none of the differences observed reached statistical significance. The two ALL patients with anomalous expression of myeloid markers did not achieve CR and had short survivals of only 1 and 3 months. The four patients with T-ALL survived 4, 4+, 16 and 26+ months and the one with B-ALL, only 3 months.

Myelosuppression was the major toxicity of the treatment but was within the expected range. In all, 18 patients (72%) had infections during the neutropaenic phase: (a) unknown organism in 12 (48%); (b) pneumonia in 4 (16%); (c) gram-negative septicaemia in 2 (8%); (d) tuberculosis in 2 (8%); (e) *Pneumocystis carinii* in 1 (4%); (f) disseminated herpes zoster in 1 (4%); and (g) dental sepsis in 1 (4%). There were no serious bleeding problems.

Non haematological toxicities were acceptable: all patients had reversible alopaecia, and nausea and vomiting were usually controllable. Mucositis was common but usually mild, except in one patient who had severe oral ulcerations following methotrexate. Peripheral neuropathy was significant in a small proportion of patients. Significant prolongation of prothrombin time occurred in two patients following L-asparaginase. Hepatitis developed in two patients and was related to 6-mercaptopurine and L-asparaginase, respectively. No patient had significant cardiotoxicity.

The deaths of 19 patients were related to uncontrolled leukaemia: 16 of these patients had received re-induction regimes. At the time of death, four patients had septicaemia (21%); four pneumonia (21%); three, disseminated fungal infection (16%); two tuberculosis (11%) and one, CNS bleeding (5%).

Discussion

Remarkable treatment results have been achieved at Sloan-Kettering Memorial Hospital with the L2, L10/L10M and L17/L17M protocols for adults with ALL [4]. These protocols are characterised by the use of multiple, active drugs that are used in various combinations, doses and schedules during the induction, consolidation and maintenance phases. The total duration of treatment is 2.5–3 years. The treatment protocols include intrathecal or intraventricular methotrexate without cranial irradiation. The overall CR rate is 83% and the median duration of remission and survival are 44 and 40 months, respectively. The remission duration and survival curves reach plateaus at 45% and 39%, respectively, with no relapses occurring after 51 months [4].

We used the L17/L17M protocol, with minor modifications, to treat our adult ALL patients; the preliminary results were disappointing. The overall response rate was only 56%, and 78.6% of the CR patients relapsed. The median disease-free survival and overall survival were only 9 and 13 months, respectively. As the follow-up periods of our surviving patients were short, with a maximal follow-up time of only 40 months, some late relapses may yet occur. The overall treatment result is expected to be worse on longer follow-up.

The causes of induction failure in our patients were reviewed. A significant proportion of our patients (28%) had PR only at the end of the course of induction chemotherapy; however, 57.1% achieved CR following second-line induction chemotherapy using moderate-dose methotrexate, vincristine, L-asparaginase and dexamethasone [6]. The inclusion of these patients increased the overall CR rate to 18/25 (72%). Hypoplastic death accounted for the remaining induction failures. A substantial proportion of the CR patients relapsed and subsequently died of uncontrolled leukaemia. Only a small minority (17%) of our patients survived beyond 2 years.

The small number of patients in this study prevented the proper determination of various prognostic factors. However, to investigate as to whether the poor treatment results observed in our patients were due to the inclusion of poor-risk patients, various known standard prognostic factors including sex, age, FAB morphology, immunophenotyping, organomegaly, white cell counts, platelet counts and CNS disease were analysed (Table 3). Although none of the differences observed reached statistical significance due to the small sample sizes, the male sex, null-ALL immunophenotype and high initial white cell counts appeared to be associated with a worse prognosis. Compared with the other series in the literature, a higher proportion of our patients belonged to the poor prognostic groups of male sex, elderly age, null cell immunophenotype and high initial white cell count [4, 11, 14]. However, this could not totally account for our poor treatment results, as our patients in the good-prognosis sub-groups apparently did not do any better.

Another possible reason to account for our inferior results was a lack of strict adherence to the protocol. It is important to adhere as closely as possible to the prescribed treatment schedule to minimize re-growth of the leukaemic populations during treatment-free intervals [4]. Confirmation requires a detailed comparison between studies of the timing and doses of the treatment actually delivered (dose intensity). However, judging from the frequencies of hypoplastic deaths and toxicities observed, our patients were probably receiving the optimal doses of the drugs within the protocol.

It is generally agreed that a high initial white cell count and L3 morphology are associated with a high risk of developing CNS leukaemia [4]. Despite the use of CNS prophylaxis, 5 of our 25 patients (20%) developed CNS leukaemia. The relatively high incidence of CNS relapses might be related to our high proportion of patients with high initial white cell counts. Indeed, four of our five CNS relapses had initial white cell counts above 30×10^9/l, the highest being 567×10^9/l. Moreover, all five patients underwent systemic leukaemia relapses either at the time of CNS relapse or shortly afterward.

More effective treatment for adult ALL remains to be explored. Clinical trials of intensive combination chemotherapy are continuing in the hope of increasing the cure rate [10, 11, 14]. Autologous or allogeneic bone marrow transplantation is still an experimental approach, but it has produced encouraging results [16].

References

1. Barnett MJ, Greaves MF, Amess JAL, Gregory WM, Rohatiner AZS, Dhaliwal HS, Slevin ML, Biruls R, Malpas JS, Lister TA (1986) Treatment of acute lymphoblastic leukaemia in adults. Br J Haematol 64: 455–468
2. Ben-Besat I, Gale RP (1984) Hybrid acute leukaemia. Leuk Res 8: 929–936
3. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Garlnick HR, Sultan C (1981) The morphological classification of acute lymphoblastic leukaemia: concordance among observers and clinical correlations. Br J Haematol 47: 533–561
4. Clarkson B, Ellis S, Little C, Gee T, Arlin Z, Mertelsmann R, Andreeff M, Kempin S, Koziner B, Chaganti R, Jhanwar S, McKenzie S, Cirrincione C, Gaynor J (1985) Acute lymphoblastic leukaemia in adults. Semin Oncol 12: 160–176
5. Durrant J (1986) Curing ALL with drugs. Hematol Rev 1: 37–48
6. Esterhay RJ Jr, Wiernik PH, Grove WR, Markus SD, Wesley MN (1982) Moderate dose methotrexate, vincristine, asparaginase and dexamethasone for treatment of adult acute lymphocytic leukaemia. Blood 59: 334–345
7. Fiere D, Extra JM, David B, Witz F, Vernand JP, Gastaut JA, Dauriac C, Pris J, Marty M (1987) Treatment of 218 adult acute lymphoblastic leukaemias. Semin Oncol 14 [Suppl 1]: 64–66
8. Henderson ES (1986) Acute leukaemia in adults. In: Hoogstraten B (ed) Hematologic malignancies. Springer-Verlag, Berlin, pp 17–29
9. Ho FCS, Loke SL, Hui PK, Todd D (1986) Immunohistological subtypes of non-Hodgkin's lymphoma in Hong Kong Chinese. Pathology 18: 426–430
10. Hoelzer D, Gale RP (1987) Acute lymphoblastic leukaemia in adults: recent progress, future directions. Semin Hematol 24: 27–39
11. Hoelzer D, Thiel E, Loffler H, Bodenstein H, Plaumann L, Buchner T, Urbanitz D, Koch P, Heimpel H, Engelhardt R, Muller U, Wendt FC, Sodomann H, Ruhl H, Herrmann F, Kaboth W, Dietzfelbinger H, Pralle H, Lunscken CH, Hellriegel KP, Spors S, Nowrousian RM, Fischer J, Fulle H, Mitron PS, Pfreundschuh M, Gorg Ch, Emmerich B, Queisser W, Meyer P, Labedzki L, Essers U, Konig H, Mainzer K, Herrmann R, Messerer D, Zwingers T (1984) Intensifed therapy in acute lymphoblastic and acute undifferentiated leukaemia in adults. Blood 64: 38–47
12. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457–481
13. Kirshner J, Preisler HD (1984) Acute lymphoblastic leukaemia: treatment. In: Goldman JM, Preisler HD (eds) Leukaemias. Butterworth's, London, pp 190–207
14. Linker CA, Levitt LJ, O'Donnell M, Ries CA, Link MP, Foreman SJ, Farbstein MJ (1987) Improved results of treatment of adult acute lymphoblastic leukaemia. Blood 69: 1242–1248
15. Prentice HG, Grob JP (1986) Acute lymphoblastic leukaemia in adults. Clin Haematol 15: 755–780
16. Prentice HG, Grob JP, Brenner MK (1986) Bone marrow transplantation in the treatment of acute lymphoblastic leukaemia. Haematol Rev 1: 49–72
17. Simon R (1986) Confidence intervals for reporting results of clinical trials. Ann Intern Med 105: 429–435
18. Stass SA, Mirro J Jr (1986) Lineage heterogeneity in acute leukaemia: acute mixed-lineage leukaemia and lineage switch. Clin Haematol 15: 811–828
19. Steinherz PG, Gaynon P, Miller Dr, Reaman G, Bleyer A, Finklestein J, Evans RG, Meyers P, Steinherz LJ, Sather H, Hammond D (1986) Improved disease free survival of children with acute lymphoblastic leukaemia at high risk for early relapse with the New York regimen – a new intensive therapy protocol: a report from the Children's Cancer Study Group. J Clin Oncol 4: 744–752
20. Zittoun R, Preisler HD (1984) Reporting treatment results in nonsolid tumours. In: Byse ME, Staquet MJ, Sylvester RJ (eds). Cancer clinical trials, methods and practice. Oxford University Press, Oxford, pp 139–156

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