Endpoints

Primary endpoints

- Dose-limiting toxicity and MTD
- Pharmacokinetics of Bortezomib

Secondary endpoints

- Complete remission rate after induction therapy
- Minimal residual disease after induction therapy

Inclusion criteria (1)

1. 1-29 years old when obtaining consent.
2. Consent to participate in this study obtained from the subject or his/her representative.
3. Diagnosed with ALL
4. Patients meeting any one of the following requirements:
   1) 1st bone marrow relapse within 36 months after the date of initial diagnosis of ALL
   2) 2nd or subsequent bone marrow relapse
   3) Bone marrow relapse after hematopoietic cell transplantation
   4) Failure to achieve remission induction with one or more therapies
5. At least 7 days elapsed from the final dose of chemotherapy to the day of enrollment.
6. ECOG Performance Status 0 to 2

Inclusion criteria (2)

7. Patients meeting the following requirements as indicated by laboratory tests within 14 days before enrollment with sufficiently preserved liver, renal, and cardiac functions.
   1) AST and ALT <= 5x ULN
   2) Serum bilirubin <= 2.0 mg/dL
   3) Creatinine <= 2x ULN
   4) 12-lead ECG indicating no abnormality requiring treatment and/or no abnormal conducting system.
8. SpO2 >= 96% and chest CT indicating no abnormal finding in the lung fields.
9. Patients who can receive PSL monotherapy and combination therapy during hospitalization.

Exclusion criteria (1)

1. Mature B-cell ALL (L3)
2. Previous treatment with Bortezomib
3. The following complications/previous histories:
   1) Concurrent infection requiring systemic treatment at enrollment.
   2) Previous cardiac disease: previous myocardial infarction/angina pectoris within 12 months before enrollment.
   3) Patients requiring oxygenation or showing respiratory insufficiency.
   4) Previous interstitial pneumonia or pulmonary fibrosis.
   5) Abnormal pulmonary function test, KL-6, SP-D, or SP-A as demonstrated by screening tests.
   6) Abnormal beta-D glucan, Candida antigen, or Aspergillosis antigen as demonstrated by screening tests.
   7) Previous fungus infection.
   8) CNS or peripheral nerve disorder.
   9) Other complications determined to seriously compromise conducting of the study (for example, uncontrollable diabetes).

Exclusion criteria (2)

4. Down syndrome
5. Active double cancer (simultaneous double cancer, and metachronous double cancer with up to a 5-year disease-free period; carcinoma in situ determined as cured with local therapy or lesions consistent with intramucosal carcinoma are not included in double cancer.)
6. Determined as difficult to participate in the study because of complicated psychiatric disease or mental symptoms.
7. Participation in other clinical studies, excluding those of ALL, within 30 days after obtaining consent.
8. Pregnant or possibly pregnant women. Breastfeeding women. Men and women providing no consent to avoiding pregnancy during the study.
9. Previous hypersensitivity to mannitol, boron, or other components of Bortezomib.
10. Patients determined as ineligible for participation in the study by an investigator/sub-investigator for other reasons.

■ Treatment plan

Intervention

In addition to the backbone induction therapy, intravenous administration of Bortezomib will be given at a dose of 1.3 or 1.0 mg/m^2 on Days 1, 4, 8, and 11.

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Treatment plan

		BZM-ALL-1																			
		PSL pre-phase																			
Day		P1	P2	P3	P4	P5	P6	P7	1	2	3	4	5	6	7	8	9	10	11	12	13	14
BZM									○			○				○			○			
PSL	60mg/m^2	○	○	○	△	△	△	△	○	○	○	○	○	○	○	○	○	○	○	○	○	○
VCR: 1.5mg/m^2									○							○						
DNR:: 30 mg/m^2											○	○										
L-asp6000U/m^2																○		○		○		
CPA:1g/m^2										○												
TIT		○																				

		BZM-ALL-1																			
Day		15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
BZM																						
PSL	60mg/m^2	○	○	○	○	○	○	○	○	○	○	○	○	○	○							
	30mg/m^2															○	○					
	10mg/m^2																	○	○			
	5mg/m^2																			○	○	○
VCR		○							○													
DNR											○	○										
L-ASP		○		○		○			○		○		○									
CPA																						
TIT		○																				

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