SUPPLEMENTAL DATA

Exposure-adjusted adverse events comparing blinatumomab with chemotherapy in advanced acute lymphoblastic leukemia

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Standard-of-Care Chemotherapy (SOC) Regimens

Patients assigned to the SOC arm received one of four regimens based on investigator's choice (see below). Once a chemotherapy regimen was initiated, the regimen was not to be changed. If indicated for toxicity or other safety reasons, dose modifications were performed as specified by the protocol.[1] A change in regimen only occurred if the criteria for discontinuation were met.

1. FLAG (fludarabine, cytarabine arabinoside, and granulocyte colony-stimulating factor) ± anthracycline-based regimen (such as idarubicin 10 mg/m^2 on days 1 and 3; fludarabine 30 mg/m^2 on days 1–5; cytarabine arabinoside 2 g/m^2 on days 1–5). For patients > 60 years of age: idarubicin 5 mg/m^2 on days 1 and 3; fludarabine 20 mg/m^2 on days 1–5; cytarabine 1 g/m^2 on days 1–5.
2. HiDAC (high-dose cytarabine arabinoside)-based regimen utilizing doses of cytarabine arabinoside of at least 1 g/m^2 or greater per day ± anthracycline and/or in combination with other drugs, such as native *E. coli* asparaginase, polyethylene glycol-asparaginase (PEG-asparaginase), vinca alkaloids, steroids, etoposide, or alkylating agents.
3. High-dose methotrexate (HDMTX)–based regimen (such as 500 mg/m^2–3 g/m^2 [infusion time up to 24 hours]) in combination with other drugs, such as native *E. coli* asparaginase, PEG-asparaginase, vinca alkaloids, steroids, etoposide, or alkylating agents.
4. Clofarabine or clofarabine-based regimens. Clofarabine use as a single agent should follow the recommended prescribing information. Clofarabine combination–based regimens should use ≥ 20 mg/m^2/day for up to 5 days.

Additional details on dose modifications, interruptions, and discontinuations for both treatments can be found in the Supplementary Materials – Protocol.[1]

REFERENCE

1. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med*. 2017;376(9):836-847.

Table S1: All grade treatment-emergent AEs of clinical interest: incidence rates[a]

	Blinatumomab (N = 267) No. of patients (%)	**SOC (N = 109) No. of patients (%)**
	Any grade	**Any grade**
Any AE	263 (99)	108 (99)
Cytokine release syndrome	43 (16)	0
Cytokine release syndrome	38 (14)	0
Hematophagic histiocytosis	4 (1)	0
Cytokine storm	1 (< 1)	0
Tumor lysis syndrome	10 (4)	1 (1)
Acute pancreatitis	1 (< 1)	1 (1)
Neurologic events	163 (61)	54 (50)
Headache	77 (29)	32 (29)
Insomnia	28 (10)	10 (9)
Tremor	26 (10)	0
Dizziness	18 (7)	8 (7)
Somnolence	14 (5)	1 (1)
Seizure	5 (2)	4 (4)
Gastrointestinal disorders	150 (56)	87 (80)
Diarrhea	58 (22)	38 (35)
Nausea	51 (19)	46 (42)
Constipation	34 (13)	28 (26)
Vomiting	33 (12)	26 (24)
Stomatitis	18 (7)	14 (13)
Abdominal pain	17 (6)	19 (17)
Dyspepsia	10 (4)	7 (6)
Infections	171 (64)	79 (72)
Cytopenias	160 (60)	79 (72)

Febrile neutropenia	64 (24)	43 (39)
Neutropenia	53 (20)	33 (30)
Thrombocytopenia	47 (18)	32 (29)
Decreased platelets	17 (6)	13 (12)
Decreased white blood cells	14 (5)	6 (6)
Decreased neutrophils	10 (4)	11 (10)
Leukopenia	10 (4)	5 (5)
Decreased lymphocytes	3 (1)	4 (4)
Lymphopenia	2 (1)	0
Elevated liver enzymes	58 (22)	27 (25)
Progressive multifocal leukoencephalopathy	2 (1)	0
Decreased immunoglobulins	26 (10)	2 (2)
Other AEs of interest		
Pyrexia	159 (60)	49 (45)
Anemia	69 (26)	46 (42)

[a]Data are summarized for all patients who received at least one dose of study treatment.
AE, adverse event; SOC, standard-of-care chemotherapy.

Table S2: All grade treatment-emergent AEs of clinical interest: relative incidence rates in cycles 1 and cycle 2

	Blinatumomab (N = 267)		**SOC (N = 109)**	
	Cycle 1 (n = 267)	**Cycle 2 (n = 151)**	**Cycle 1 (n = 109)**	**Cycle 2 (n = 28)**
Any AE, n (%)	**260 (97)**	**122 (81)**	**107 (98)**	**28 (100)**
Cytokine release syndrome	40 (15)	5 (3)	0	0
Cytokine release syndrome	**36 (13)**	**5 (3)**	**0**	**0**
Hematophagic histiocytosis	3 (1)	0	0	0
Cytokine storm	1 (< 1)	0	0	0
Tumor lysis syndrome	**9 (3)**	**0**	**1 (1)**	**0**
Acute pancreatitis	1 (< 1)	0	0	1 (4)
Neurologic events	140 (52)	45 (30)	52 (48)	6 (21)
Headache	61 (23)	13 (9)	30 (28)	3 (11)
Insomnia	21 (8)	5 (3)	10 (9)	1 (4)
Tremor	24 (9)	4 (3)	0	0
Dizziness	14 (5)	2 (1)	7 (6)	1 (4)
Somnolence	12 (4)	2 (1)	1 (1)	0
Seizure	5 (2)	0	4 (4)	0
Gastrointestinal disorders	132 (49)	38 (25)	82 (75)	20 (71)
Diarrhea	39 (15)	16 (11)	35 (32)	4 (14)
Nausea	39 (15)	13 (9)	40 (37)	13 (46)
Constipation	32 (12)	3 (2)	24 (22)	8 (29)
Vomiting	14 (5)	10 (7)	23 (21)	8 (29)
Stomatitis	10 (4)	6 (4)	11 (10)	2 (7)
Abdominal pain	11 (4)	3 (2)	17 (16)	2 (7)
Dyspepsia	6 (2)	3 (2)	6 (6)	1 (4)
Infections	129 (48)	43 (28)	71 (65)	14 (50)
Cytopenias	134 (50)	32 (21)	78 (72)	20 (71)

Febrile neutropenia	58 (22)	6 (4)	40 (37)	10 (36)
Neutropenia	33 (12)	16 (11)	32 (29)	8 (29)
Thrombocytopenia	43 (16)	5 (3)	31 (28)	9 (32)
Decreased platelets	14 (5)	3 (2)	11 (10)	3 (11)
Decreased white blood cells	11 (4)	3 (2)	5 (5)	2 (7)
Decreased neutrophils	7 (3)	1 (1)	9 (8)	5 (18)
Leukopenia	10 (4)	2 (1)	4 (4)	1 (4)
Decreased lymphocytes	2 (1)	0	4 (4)	0
Lymphopenia	1 (< 1)	0	0	0
Elevated liver enzymes	55 (21)	10 (7)	26 (24)	4 (14)
Progressive multifocal leukoencephalopathy	1 (< 1)	0	0	0
Decreased immunoglobulins	7 (3)	7 (5)	2 (2)	0
Other AEs of interest				
Pyrexia	147 (55)	37 (25)	43 (39)	11 (39)
Anemia	66 (25)	5 (3)	45 (41)	9 (32)

AE, adverse event; SOC, standard-of-care chemotherapy.

Table S3: Exposure-adjusted event rates for treatment-emergent AEs of clinical interest

	Blinatumomab (N = 267)		SOC chemotherapy (N = 109)		
Total treatment exposure	**89.0 years**		**14.8 years**		
	No. of events	**Exposure-adjusted event rate[b]**	**No. of events**	**Exposure-adjusted event rate[b]**	***P*-value[a]**
All AEs	4108	46.16	2037	137.64	<0.001
Cytokine release syndrome	56	0.63	0	0	<0.001
Cytokine release syndrome	49	0.55	0	0	0.001
Hematophagic histiocytosis	6	0.07	0	0	0.174
Cytokine storm	1	0.01	0	0	—
Tumor lysis syndrome	10	0.11	1	0.07	0.603
Acute pancreatitis	1	0.01	1	0.07	0.232
Neurologic events	420	4.72	110	7.43	<0.001
Headache	101	1.14	39	2.64	<0.001
Insomnia	38	0.43	12	0.81	0.068
Tremor	36	0.40	0	0	0.001
Dizziness	20	0.23	8	0.54	0.051
Somnolence	19	0.21	1	0.07	0.180
Seizure	5	0.06	4	0.27	0.029
Gastrointestinal disorders	402	4.52	339	22.91	<0.001
Diarrhea	72	0.81	49	3.31	<0.001
Nausea	71	0.80	69	4.66	<0.001
Constipation	45	0.51	34	2.30	<0.001
Vomiting	35	0.39	40	2.70	<0.001
Stomatitis	19	0.21	16	1.08	<0.001
Abdominal pain	19	0.21	25	1.69	<0.001
Dyspepsia	11	0.12	7	0.47	0.010

Infections	388	4.36	180	12.16	<0.001
Cytopenias	467	5.25	355	23.99	<0.001
Febrile neutropenia	83	0.93	54	3.65	<0.001
Neutropenia	108	1.21	52	3.51	<0.001
Thrombocytopenia	112	1.26	111	7.50	<0.001
Decreased platelets	54	0.61	73	4.93	<0.001
Decreased white blood cells	36	0.40	12	0.81	0.050
Leukopenia	30	0.34	5	0.34	0.996
Decreased neutrophils	23	0.26	28	1.89	<0.001
Decreased lymphocytes	3	0.03	8	0.54	<0.001
Lymphopenia	3	0.03	0	0	—
Elevated liver enzymes	176	1.98	102	6.89	<0.001
Progressive multifocal leukoencephalopathy	4	0.04	0	0	—
Decreased immunoglobulins	31	0.35	2	0.14	0.135
Other AEs					
Pyrexia	335	3.76	75	5.07	0.024
Anemia	204	2.29	146	9.87	<0.001

[a]*P*-value comparing blinatumomab vs SOC from a Poisson regression model using number of AEs as the dependent variable and log(exposure time) as offset.

[b]Per patient-year.

Blue favors blinatumomab arm; red favors SOC.

AE, adverse event; No., number; SOC, standard-of-care chemotherapy.