

Supplement

Presentation of childhood leukemia: systematic review and meta-analysis

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eSearch: Electronic database search strategy

A. Medline search strategy for leukaemia (last conducted Dec 2014)

1. leukemia/ or exp leukemia, lymphoid/ or exp leukemia, myeloid/
2. (leukemia* or leukaemia*).tw.
3. 1 or 2
4. (sign or signs or symptom*).tw.
5. ((clinical or biological or physical) adj5 (feature* or present* or characteristic* or manifestation*)).tw.
6. (present* adj5 (feature* or characteristic*)).tw.
7. present*.ti.
8. 4 or 5 or 6 or 7
9. 3 and 8
10. (child* or infan* or toddler* or adolescent* or teenage* or pediatric* or paediatric*).tw.
11. adolescent/ or exp child/ or exp infant/
12. 11 or 10
13. 9 and 12

B. Medline search strategy for cancer (last conducted Dec 2014):

1. (cancer* or neoplasm* or tumor* or tumour* or malignan*).ti.
2. (child* or adolescent* or teenage* or infan* or toddler* or pediatric* or paediatric*).ti.
3. 1 and 2
4. (sign or signs or symptom*).tw.
5. ((clinical or biological or physical) adj5 (feature* or present* or characteristic* or manifestation*)).tw.
6. (present* adj5 (feature* or characteristic*)).tw.
7. present*.ti.
8. 4 or 5 or 6 or 7
9. 8 and 3

C. Embase search strategy for leukaemia (last conducted Dec 2014)

1. exp Leukemia/

2. (leukemia* or leukaemia*).tw.
3. 1 or 2
4. (sign or signs or symptom*).tw.
5. ((clinical or biological or physical) adj5 (feature* or present* or characteristic* or manifestation*)).tw.
6. (present* adj5 (feature* or characteristic*)).tw.
7. clinical feature/ or symptom/
8. present*.ti.
9. 4 or 5 or 6 or 7 or 8
10. (child* or infan* or toddler* or adolescen* or teenage* or pediatric* or paediatric*).tw.
11. groups by age/ or adolescent/ or child/ or preschool child/ or school child/ or infant/
12. 11 or 10
13. 9 and 12 and 3

D. Embase search strategy for cancer (last conducted Dec 2014)

1. exp Cancer/
2. cancer*.tw.
3. 1 or 2
4. (sign or signs or symptom*).tw.
5. ((clinical or biological or physical) adj5 (feature* or present* or characteristic* or manifestation*)).tw.
6. (present* adj5 (feature* or characteristic*)).tw.
7. clinical feature/ or symptom/
8. present*.ti.
9. 4 or 5 or 6 or 7 or 8
10. (child* or infan* or toddler* or adolescen* or teenage* or pediatric* or paediatric*).tw.
11. groups by age/ or adolescent/ or child/ or preschool child/ or school child/ or infant/
12. 11 or 10
13. 9 and 12 and 3

eTable 1: Quality assessment of studies meeting eligibility criteria for potential inclusion

STUDY	1. CASE DEFINITION		2. CASE SELECTION				3. DATA SELECTION			INCLUDE PAPER?
	Adequate defn? (=bone marrow criteria)	Overall acceptable /not	Clear baseline characteristics? (eg. participants' age and sex)	Representative cohort?	Adequate ascertainment? (eg. consecutive cases?)	Overall acceptable/not	Standardised collection? (=use of proforma)	Objective measurement? (eg. ultrasound findings)	Overall acceptable/not	
Ali Al-Barazanchi (2005)	Y	Y	Y	Unclear	Unclear	N	Unclear	Unclear	N	N
Arico (1993)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	N	Y
Arya (1995)	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	Y
Atay (2005)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	N	Y
Bernbeck (2009)	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	Y
Biswas (2009)	Y	Y	Y	Y	Unclear	Y	Unclear	Y	Y	Y
Castro-Malaspina (1983)	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	Y
Castro-Malaspina (1984)	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	Y
Chan (1981)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	Y	Y
Chang (2003)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	Y	Y
Chang (2004)	Y	Y	Y	Y	Unclear	Y	Unclear	Y	Y	Y
Choi (1976)	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	Y
Da Costa Moraes (2008)	Y	Y	Y	Y	Y	Y	Unclear	Unclear	N	Y
Das (1973)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	N	Y
Drozynska (2002)	Y	Y	Y	Y	Unclear	Y	Unclear	Y	Y	Y
Garcia Calatayud (2003)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	N	Y
Grimes (2007)	N	N	Y	Y	Y	Y	Unclear	Unclear	N	N

Hasanbegovic (2006)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	N	Y
Hassan (1992)	Y	Y	Y	Y	Y	Y	Y	Unclear	Y	Y
Karimi (2008)	Y	Y	Y	Y	Unclear	Y	Y	Y	Y	Y
Klinowska (1992)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	N	Y
La Grutta (1980)	Y	Y	Y	Y	Unclear	Y	Y	Y	Y	Y
Liu (2010)	Y	Y	Y	Y	Unclear	Y	Unclear	Y	Y	Y
Ma (1997)	Y	Y	Y	Y	Y	Y	Unclear	Unclear	N	Y
Meighan (1963)	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	Y
Meighan (1964)	Y	Y	Y	Y	Y	Y	Unclear	Unclear	N	Y
Millot (2005)	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	Y
Owen (1992)	Y	Y	Y	Y	Y	Y	Unclear	Y	Y	Y
Paredes-Aguilera (2003)	Y	Y	Y	Y	Y	Y	Unclear	Unclear	N	Y
Rajarajeswari (1980)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	N	Y
Revesz (1985)	Y	Y	Y	Y	Y	Y	Unclear	Unclear	N	Y
Robazzi (2007)	Y	Y	Y	Y	Unclear	Y	Unclear	Unclear	N	Y
Sinigaglia (2008)	Y	Y	Y	Y	Y	Y	Unclear	Unclear	Y	Y
Thulesius (2000)	Y	Y	Y	Y	Y	Y	Unclear	Unclear	N	Y
Zahid (1996)	Y	Y	Y	Y	Unclear	Y	Y	Unclear	Y	Y

eTable 2: Signs and symptoms in children with leukemia with <10% prevalence

Feature	Pooled proportion (%)	(95% CI)	No. of participants	No. of studies
Zanthomata	9	(3 - 20)	9	3
Papilloedema	8	n/a	3	1
Melaena	7	n/a	5	1
Nausea/vomiting	7	(0 - 17)	7	2
Asymptomatic	6	(3 - 10)	24	6
Convulsions	6	n/a	6	1
Cough	6	(0 - 14)	8	3
Heart failure	6	(3 - 11)	3	2
Jaundice	6	(0 - 14)	9	2
CNS* symptoms	5	(2 - 8)	36	4
Headache	5	(3 - 7)	27	7
Menorrhagia	5	n/a	9	1
Night sweats	5	n/a	9	1
Chest pain	5	(2 - 8)	11	2
Gum hypertrophy	5	(1 - 10)	23	3
Neck swelling	5	(0 - 11)	15	3
Collapsed vertebra	4	n/a	1	1
Mediastinal mass	4	(2 - 5)	21	4
Sternal tenderness	4	n/a	3	1
SVCO**	4	n/a	10	1
Café au lait spots	4	(3-12)	3	2
Diarrhoea	4	(0 - 8)	10	3
Back pain	3	n/a	1	1
Erythema nodosum	3	n/a	1	1
Paraplegia	3	n/a	2	1
Priapism	3	(0 - 5)	4	4
Visual disturbance	3	n/a	1	1
Dizziness	3	(1 - 4)	12	2
Haematuria	3	(0 - 6)	6	2
Amenorrhoea	2	n/a	1	1
Ascites	2	(0 - 4)	7	4
Fracture	2	n/a	1	1
Hilar lymphadenopathy	2	n/a	8	1

Mass	2	n/a	1	1
Hearing disturbance	2	(1 - 5)	2	2
Meningism	2	(0 - 5)	11	3
Pleural effusion	2	(0 -4)	3	2
Proptosis	2	(1 - 4)	11	3
Bladder dysfunction	1	n/a	1	1
Forearm masses	1	n/a	1	1
Haematemesis	1	n/a	1	1
Ovarian mass	1	n/a	2	1
CN*** palsy	1	(0 - 30)	4	2
Mandibular swelling	1	(0 - 3)	6	3
Testicular manifestations	1	(1 - 2)	3	2
Osteomyelitis	0	n/a	1	1
Pericardial effusion	0	n/a	1	1
Pericarditis	0	n/a	1	1
Refusal to walk	0	n/a	2	1
Renal involvement	0	n/a	1	1

*Central nervous system

** Superior vena cava
obstruction

*** Cranial nerve

eTable 3: Subgroup analyses in children with leukemia by leukemia type, income status, and year of study

Presenting feature	OVERALL		SUBGROUP ONE: INCOME				SUBGROUP TWO: AGE				SUBGROUP THREE: LEUKEMIA TYPE			
	Pooled proportion (95% CI)	I2 (p-value)	1. High income		2. Middle/low income		1. 1990 - current		2. > 1990		1. Acute		2. Chronic	
			Pooled proportion (95% CI)	I2 (p-value)	Pooled proportion (95% CI)	I2 (p-value)	Pooled proportion (95% CI)	I2 (p-value)	Pooled proportion (95% CI)	I2 (p-value)	Pooled proportion (95% CI)	I2 (p-value)	Pooled proportion (95% CI)	I2 (p-value)
Infiltrative (organomegalies)														
Hepatomegaly	64 (53-75)	98 (0)	63 (49 - 77)	96 (0)	65 (49 - 81)	98 (0)	64 (50 - 77)	97 (0)	65 (50 - 79)	97 (0)	71 (59 - 82)	95 (0)	54 (28 - 79)	95 (0)
Splenomegaly	61 (48-73)	98 (0)	76 (67 - 85)	93 (0)	51 (36 - 64)	98 (0)	60 (43 - 77)	98 (0)	62 (42 - 83)	99 (0)	56 (40 - 73)	98 (0)	77 (62 - 92)	86 (0)
Hepatosplenomegaly	42 (24 - 100)	100 (0)	42 (0 - 100)	100 (0)	n/a	n/a	n/a	n/a	n/a	n/a	42 (0 - 100)	100 (0)	n/a	n/a
Lymphadenopathy	41 (32 - 51)	97 (0)	36 (22 - 50)	98 (0)	47 (37 - 58)	93 (0)	45 (33 - 57)	96 (0)	35 (20 - 50)	98 (0)	52 (42 - 62)	92 (0)	26 (7 - 46)	93 (0)
Haemorrhagic														
Bruising	52 (37 - 66)	20 (0.27)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	52 (37 - 66)	20 (0.27)	n/a	n/a
Bruising/petechiae	42 (36 - 49)	0 (0.57)	n/a	n/a	42 (36 - 49)	0 (0.57)	n/a	n/a	n/a	n/a	42 (36 - 49)	0 (0.57)	n/a	n/a
Bleeding tendency	38 (30 - 46)	90 (0)	33 (23 - 43)	85 (0)	42 (29 - 56)	93 (0)	33 (25 - 40)	79 (0)	47 (38 - 56)	81 (0)	48 (34 - 61)	88 (0)	27 (19 - 35)	37 (0.16)
Cutaneous/mucosal bleeding			n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Cutaneous bleeding	26 (14 - 38)	92 (0)	26 (14 - 38)	92 (0)	n/a	n/a	n/a	n/a	28 (8 - 48)	96 (0)	26 (14 - 38)	92 (0)	n/a	n/a
Petechiae/purpura	25 (14 - 37)	92 (0)	25 (3 - 47)	96 (0)	25 (13 - 38)	83 (0)	23 (10 - 35)	91 (0)	34 (13 - 55)	91 (0)	30 (19 - 40)	85 (0)	6 (0 - 17)	39 (0.2)
Mucosal bleeding (e.g. gums)	25 (16 - 34)	91 (0)	15 (9 - 21)	75 (0.01)	38 (19 - 57)	89 (0)	34 (16 - 53)	91 (0)	n/a	n/a	25 (6 - 34)	91 (0)	n/a	n/a
Epistaxis	10 (2 - 18)	48 (0.15)	n/a	n/a	10 (2 - 18)	48 (0.15)	10 (2 - 18)	48 (0.15)	n/a	n/a	11 (0 - 23)	74 (0.05)	n/a	n/a
Infective														
Fever	53 (45-62)	97 (0)	37 (26 - 47)	95 (0.04)	70 (62 - 77)	90 (0)	37 (26 - 48)	95 (0)	70 (62 - 77)	90 (0)	62 (51 - 73)	95 (0)	31 (13 - 49)	91 (0)
Recurrent infections	49 (16 - 81)	99 (0)	48 (12 - 85)	99 (0)	n/a	n/a	61 (55 - 68)	96 (0)	30 (0 - 84)	98 (0)	49 (16 - 81)	99 (0)	n/a	n/a
Respiratory symptoms	22 (1 - 43)	97 (0)	22 (1 - 43)	97 (0)	n/a	n/a	24 (0 - 72)	95 (0)	n/a	n/a	22 (1 - 43)	97 (0)	n/a	n/a
URTI	20 (9 - 31)	85 (0)	36 (23 - 49)	13 (0.28)	12 (1 - 23)	86 (0)	20 (9 - 31)	85 (0)	n/a	n/a	6 (0 - 12)	n/a	19 (0 - 41)	74 (0.05)
Sore throat	11 (3 - 25)	95 (0)	11 (0 - 25)	95 (0)	n/a	n/a	n/a	n/a	11 (0 - 25)	95 (0)	11 (0 - 25)	95 (0)	n/a	n/a

Musculoskeletal (MSK)														
Limb pain	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Bone pain	26 (17 - 35)	97 (0)	10 (5 - 15)	78 (0)	33 (20 - 46)	97 (0)	32 (18 - 45)	97 (0)	15 (7 - 22)	89 (0)	23 (19 - 26)	12 (0.34)	16 (3 - 36)	79 (0.03)
MSK impairment	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Bone and/or joint pain	19 (13 - 25)	76 (0)	17 (9 - 26)	83 (0)	20 (14 - 25)	0 (0.43)	22 (12 - 31)	76 (0)	15 (8 - 22)	71 (0.02)	19 (11 - 28)	86 (0)	19 (8 - 30)	55 (0.11)
Joint pain	15 (5 - 25)	96 (0)	19 (11 - 27)	57 (0.1)	13 (0 - 28)	98 (0)	15 (1 - 29)	97 (0)	14 (0 - 34)	97 (0)	21 (0 - 49)	98 (0)	n/a	n/a
Limp	11 (0 - 21)	94 (0.05)	6 (0 - 12)	72 (0.03)	n/a	n/a	11 (0 - 21)	94 (0)	n/a	n/a	n/a	n/a	n/a	n/a
Systemic														
Pallor	54 (40-69)	99 (0)	34 (15 - 52)	98 (0)	73 (61 - 85)	96 (0)	63 (50 - 75)	96 (0)	42 (19 - 64)	99 (0)	60 (44 - 76)	97 (0)	57 (0 - 100)	99 (0)
Fatigue	46 (28 - 64)	97 (0)	39 (8 - 71)	98 (0)	47 (0 - 94)	98 (0)	43 (23 - 63)	97 (0)	n/a	n/a	42 (18 - 66)	98 (0)	n/a	n/a
Malaise/fatigue	31 (7 - 56)	97 (0)	41 (11 - 70)	93 (0)	n/a	n/a	n/a	n/a	37 (0 - 77)	97 (0)	32 (0 - 87)	98 (0)	31 (0 - 64)	92 (0)
Weakness/fatigue	27 (18 - 36)	94 (0)	26 (18 - 34)	84 (0)	29 (9 - 50)	97 (0)	42 (20 - 63)	95 (0)	15 (7 - 23)	87 (0)	25 (16 - 33)	n/a	n/a	n/a
Oedema	15 (10 - 20)	0 (0.58)	n/a	n/a	15 (10 - 21)	0 (0.51)	20 (0 - 45)	17 (0.27)	15 (10 - 22)	0	14 (7 - 20)	0 (0.6)	n/a	n/a
Gastro-intestinal														
Anorexia/weight loss	29 (16 - 42)	97 (0)	22 (15 - 28)	77 (0)	43 (14 - 73)	98	24 (15 - 33)	90 (0)	38 (4 - 73)	99 (0)	31 (15 - 48)	98	19 (13 - 26)	0 (0.65)
Abdominal symptoms	20 (9 - 31)	89 (0)	20 (9 - 31)	89 (0)	n/a	n/a	38 (24 - 52)	83 (0)	14 (5 - 23)	89 (0)	21 (3 - 34)	82	38 (24 - 52)	0 (0.81)
Abdominal pain	12 (7 - 16)	49 (0)	15 (7 - 24)	64 (0.02)	10 (6 - 15)	0	15 (10 - 21)	14 (0.33)	8 (5 - 11)	12 (0.29)	11 (7 - 15)	0	n/a	n/a
Abdominal distension	11 (3 - 18)	87 (0.1)	8 (0 - 16)	89 (0)	12 (3 - 21)	87	8 (1 - 15)	82 (0)	n/a	n/a	30 (0 - 84)	92	9 (1 - 16)	0 (0.43)
Cutaneous														
Rash	35 (22 - 48)	72	33 (16 - 49)	77 (0)	43 (25 - 62)	29	41 (27 - 56)	62 (0.03)	20 (9 - 31)	0 (0.6)	31 (19 - 43)	60	n/a	n/a
Pyoderma	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Nodules	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Skin infiltration	12 (11 - 36)	97	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	12 (0 - 36)	97	n/a	n/a