BMJ Open

Plasma concentration guided dosing of drugs used for the treatment of childhood leukaemias: protocol for a systematic review

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To cite: van Dyk M, Boylan C, Michelet R, *et al*. Plasma concentration guided dosing of drugs used for the treatment of childhood leukaemias: protocol for a systematic review. *BMJ Open* 2022;**12**:e053308. doi:10.1136/bmjopen-2021-053308

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-053308).

Received 10 May 2021
Accepted 19 November 2021

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ABSTRACT

Introduction Childhood leukaemia is the most common type of cancer in children and represents among 25% of the diagnoses in children <15 years old. Childhood survival rates have significantly improved within the last 40 years due to a rapid advancement in therapeutic interventions. However, in high-risk groups, survival rates remain poor. Pharmacokinetic (PK) data of cancer medications in children are limited and thus current dosing regimens are based on studies with small sample sizes. In adults, large variability in PK is observed and dose individualisation (plasma concentration guided dosing) has been associated with improved clinical outcomes; whether this is true for children is still unknown. This provides an opportunity to explore this strategy in children to potentially reduce toxicities and ensure optimal dosing. This paper will provide a protocol to systematically review studies that have used dose individualisation of drugs used in the treatment of childhood leukaemias.

Methods and analysis Systematic review methodology will be applied to identify, select and extract data from published plasma guided dosing studies conducted in a paediatric leukaemia cohort. Databases (eg, Ovid Embase, Ovid MEDLINE, Ovid Cochrane) and clinical trial registries (CENTRAL, ClinicalTrials.gov and ISRCTN) will be used to perform the systematic literature search (up until February 2021). Only full empirical studies will be included, with primary clinical outcomes (progression-free survival, toxicities, minimal residual disease status, complete cytogenetic response, partial cytogenetic response and major molecular response) being used to decide whether the study will be included. The quality of included studies will be undertaken, with a subgroup analysis where appropriate.

Ethics and dissemination This systematic review will not require ethics approval as there will not be collection of primary data. Findings of this review will be made available through publications in peer-reviewed journals and conference presentations. Gaps will be identified in current literature to inform future-related research.

PROSPERO registration number CRD42021225045.

Strengths and limitations of this study

- This review will be *the first* to summarise available studies regarding dose individualisation of drugs used to treat childhood leukaemias, and how they have been used in clinical practice.
- This review will assess associations between specific chemotherapeutic plasma concentration data and clinical outcomes.
- Our review includes a focus on small molecule targeted therapies, monoclonal antibodies and chemotherapies encompassing many of the current treatment options for childhood leukaemia, thereby forming an up-to-date analysis of treatments available for our study indication.
- This review assesses available information about the associations between clinical outcome data and the pharmacokinetics of drugs used to treat childhood leukaemia and how it is being clinically applied; this type of data are scarce.

INTRODUCTION

Globally, leukaemia is the most common (25%) childhood cancer with the highest incidence in children aged 1–4 years.[1] In 2018, it was estimated that worldwide more than 29 000 childhood cancer deaths were due to leukaemia.[2] Acute lymphoblastic leukaemia (ALL) is the most common childhood leukaemia; the 5-year survival rate within low risk and standard risk groups has improved to 90% during the past 40 years due to increased participation in studies, allowing clinicians to build on previous successes.[3] However, 5-year survival rates within paediatric patients with ALL identified as high risk or very high risk remain between 40% and 50%.[4] Therapies have become more risk stratified with the potential to reduce toxicity and long-term

sequelae.[3 4] For childhood acute leukaemias (ALL and acute myeloid leukaemia; AML) treatments largely consists of protocolised combination pharmacotherapy including standard chemotherapy, targeted therapy and corticosteroids (further detailed in online supplemental appendix 1). For ALL, these therapies are used over the course of 2–3 years.[5 6] For AML the therapy duration is much shorter lasting for approximately 6 months. Small molecule kinase inhibitors are commonly used in specific cancers such as Philadelphia chromosome positive chronic myeloid leukaemia (CML) and ALL.[5 6] In addition, bispecific T cell engagers are now available for the first-line therapy of paediatric patients with ALL and for management of relapse or refractory disease.[7] Similarly, monoclonal antibodies have now been incorporated into chemotherapeutic regimens to improve outcomes in children with AML.[6] It is well recognised that these novel treatment regimens may have short-term toxicities[7] and that long-term effects are still unknown[8]

The accepted practice of paediatric dosing is either by body surface area or weight-based dosing (ie, mg/kg) due to concerns related to the narrow therapeutic index of cytotoxic anticancer drugs and the assumed relationships between body size and drug disposition in these patients.[9] Many factors that may need to be considered include the maturity of drug metabolising enzyme systems, differences in enzyme activity that may be genetic, the effects of obesity and concomitant medications and diet.[10] Our rationale for assessing data on plasma concentration guided dosing of drugs used in the treatment of childhood leukaemia include: (1) It is well recognised that pharmacokinetic (PK) data of anticancer drugs in children are extremely limited and thus dosing regimens are often extrapolated from adult data and based on paediatric studies with a small sample size;[11 12] (2) When administering drugs, there are notable differences in PK and pharmacodynamic properties between adults and children such as age-related differences in the way drugs are absorbed, distributed, metabolised and eliminated;[13] (3) There is an opportunity to assess the current state of the art for the optimal dosing in paediatric patients with leukaemia[14] as in adults with leukaemia (eg, imatinib TDM for CML), therapeutic drug monitoring (TDM), using target plasma concentration guided dosing has been demonstrated to optimise exposure and is associated with favourable treatment outcomes (response and survival).[15] These target concentrations have not been defined for many drugs used for the treatment of leukaemia in children; and (4) In addition, as childhood ALLs require cancer chemotherapy on an ongoing basis for many months, adherence to prescribed therapies may not be consistent or unexpected toxicities may occur with routine dosing. TDM as part of plasma concentration guided dosing provides additional benefits of monitoring for adherence to prescribed therapies and optimising dosing. Furthermore, the relationship between target plasma drug concentration and outcome/toxicity and whether plasma concentration guided dosing will improve the outcome of the treatment has been poorly investigated in childhood leukaemia. Finally, this review will assess the evidence and the quality of the evidence for plasma guided dosing of all drugs used for the treatment of childhood leukaemia.

RESEARCH AIMS AND OBJECTIVES

This study aims to conduct a systematic review of the approach of using target plasma concentration guided dosing for drugs used to treat childhood leukaemia's.

METHODS AND DESIGN

Patient and public involvement

There will be no patient or public participation involvement as this systematic review is capturing previous findings. However, to increase insight and perspective from people living with cancer, we involve members from our consumer engagement group to provide feedback on our research study design. Therefore, we would like to acknowledge Mr Ryan Hodges, from our consumer engagement group, who have provided verbal feedback on our study design for this protocol paper and will continue that into the systematic literature review (SLR) too.

Inclusion criteria

- Studies investigating any medications used to treat childhood leukaemias, both approved or off-label (chemotherapy, targeted therapies, monoclonal antibodies,) that report on plasma concentration guided dosing strategies in a paediatric population (0–21 years, including neonates, infants and young children).
- Studies that directly compare monitoring of medications used for the treatment of leukaemia in adult cohorts that are extrapolated to paediatric cohorts.
- Retrospective, prospective, case series, descriptive, quantitative or simulation-based studies reporting plasma concentrations in paediatrics.
- Trial-based or non-trial-based studies, randomised clinical trials or non-randomised controlled studies.
- Studies published in conference abstracts.
- Studies published in the English language.

Exclusion criterion

- Studies that only included adult populations.
- Studies that are not reporting data on plasma concentrations, (modelling, simulation based, therapeutic drug monitoring, plasma dosing, serum adjusted levels).
- Studies that have a non-clinical experimental design or written as reviews (reviews may be used as a data source to find relevant studies).
- Study will be excluded if it does not relate to the condition or domain being reviewed (childhood

leukaemia) or does not include a drug therapy used to treat leukaemias.

Condition or domain

Condition or domain under study is childhood leukaemia.

Population

Real patients or data simulated from paediatric patients of any sex and race, inpatients or outpatients, who are treated with any antileukaemia agents such as chemotherapies and targeted therapies such as kinase inhibitors and monoclonal antibodies.

Outcome measures

Relevant primary outcomes will include clinical outcomes such as patient survival (eg, overall survival and relapse-free survival). Where there is opportunity to be more specific, secondary outcomes such as rates of major molecular response (MMR), complete cytogenetic response (CCyR) and partial cytogenetic response (PCyR) in the case of paediatric CML and achievement of minimal residual disease (MRD) negativity in paediatric ALL will also be assessed. Where possible, toxicity data and duration of therapies will also be reported.

Exposures/interventions

The primary exposure in this review will be plasma concentrations of any kinase inhibitor, monoclonal antibody or chemotherapy used for the treatment of leukaemia in paediatric patients. Any intervention aimed at individualising drug dosage (toxicity adjusted dosing, model-informed precision dosing, genotyping or phenotyping approaches) will also be included as secondary exposures.

Study design

The systematic review will consider quantitative studies of good quality (based on quality assessment below) published from the databases' inception until February 2021. The searches will be rerun immediately prior to the final analyses and any further studies retrieved will be screened for inclusion.

Search strategies

The following steps will be undertaken to perform the search strategy. An initial focused search of MEDLINE (PubMed) and Google Scholar will be undertaken. An analysis of the text words contained in the title and abstracts, and the index terms assigned to the results will then be used to develop the Medical Subject Headings (MeSH) and key terms for the search. Four predefined search concepts relating to the research question will be used; these are detailed below:

- Concept 1: will include all MeSH, substance names and key terms for all approved and off-label medications for treating childhood leukaemias.
- Concept 2: will focus on the disease area and will include the MeSH of leukaemia as well as key terms including cancer, leukaemia, oncology and neoplasms.
- Concept 3: will be interventions such as precision-based dosing. MeSH terms include precision medicine and drug monitoring; additional key terms will include individualised dosing, plasma guided dosing, therapeutic drug monitoring, plasma concentrations and optimal dosing.
- Concept 4: will focus on the patient cohort. MeSH terms include adolescent and child and an extensive set of key terms including paediatric, childhood, neonatal, infant and youth.

A detailed search strategy applied in MEDLINE is provided in the online supplemental appendix 1.

Second, the search will be adapted, using all identified keywords and index terms, specifically for the following databases: Ovid Embase (1974+), Ovid MEDLINE (1946+), Ovid Cochrane (2005+), Ovid EmCare (1995+), EBSCO CINAHL Plus (1936+), Scopus (1996+), ClinicalTrials.gov (2000+) and Web of Science (1945+). Finally, we will undertake backward and forward citation chaining of relevant documents (including Food and Drug administration, Therapeutic Goods Aministration and European Medicines Agency documents).

Study selection

Titles and abstracts from each database will be screened and relevant records selected for a full-text appraisal. The study selection process will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11] Search results will be exported into the citation management software EndNote, and into the systematic review software, Covidence. Titles and abstracts will be distributed among three independent reviewers for screening against the inclusion criteria. The strength of agreement between reviewers will be estimated by calculating the intraclass correlation coefficient.[16] Two reviewers will then assess the full text of selected articles for eligibility. Any disagreement or conflicting views will be resolved by discussion or the final judgement of a third reviewer. Included articles will then progress to quality assessment or critical appraisal, data extraction and analysis.

Quality assessment

The review will include studies with differences in study design, therefore, the selected papers will be assessed for methodological validity using a Mixed Methods Appraisal Tool.[17] Studies will not be excluded based on the outcome of the quality assessment as the assessment is aimed to offer general information about the quality and strength of the existing frameworks and evidence of plasma concentration guided dosing of drugs used to treat leukaemia in children.

Data extraction

Two reviewers will screen the initial articles based on title and abstract in Covidence. The reviewers will independently perform a full-text review on the identified articles against the inclusion and exclusion criteria. The

data extracted will include specific details about the dosing strategies (ie, standard (one-size fits-all), body weight-based, body surface area-based, plasma concentration guided dosing strategies), the settings, the population and sample size and outcomes as well as details of the results. In the case that the data are not interpretable, citing articles will be explored and if this information is insufficient, the study will be excluded.

Strategy for data synthesis

Following data extraction, the reviewers will provide a narrative synthesis of the results from the included studies, structured around general characteristics, characteristics of the intervention programmes and treatment endpoints concluded in the study (progression-free survival, overall survival, disease-free survival, relapse-free survival, event-free survival, death, toxicity and disease-specific endpoints such as MMR, CCyR, PCyR and MRD). The statistical analyses of the data conducted by the included studies will also be briefly discussed in this review.

Analysis

We are interested in the relationship between plasma concentrations (or exposures) of drugs used to treat leukaemias and clinical outcomes in children. Therefore, a narrative synthesis of the outcomes of the selected studies will be presented in the final review. The plasma concentration parameter (eg, minimum plasma concentration: C_{min}, maximum plasma concentration: C_{max} or area under the plasma concentration versus time curve: AUC), control group, sample size, demographic and clinical characteristics and clinical endpoints will be included.

ETHICS AND DISSEMINATION

This systematic review will not require ethics approval as there will not be any collection of primary data. Findings of this review will be disseminated through publications in peer-reviewed journals, presentations at workshops or conferences and sharing through a media release.

CONCLUSION

This systematic review will assess and summarise available studies regarding associations between plasma concentration data for drugs used to treat childhood leukaemia, and clinical outcomes. It will specifically review the evidence of plasma concentration guided dosing in children with leukaemia and how they have been used in clinical practice. It will provide support for, or against, the hypothesis that individualised dosing of therapies used to treat childhood leukaemia could improve patient outcomes due to optimised patient dosing and reduction in the rate of adverse events/toxicities.

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Funding MvD reports grants from Cancer Council SA/Flinders University (ECR Beat Cancer/10686). CK reports grants from an Industry Consortium (AbbVie Deutschland GmbH & Co. KG, AstraZeneca GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Grünenthal GmbH, F. Hoffmann-La Roche Ltd, Merck KGaA and SANOFI) for the PharMetrX programme/grant number: NA, The Federal Ministry of Education/grant number: NA and Research and the European Commission within in the Horizon 2020 framework programme/grant number: NA.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 1: Medline Search Strategy

Searches downloaded by Nikki May – SA Health Library Service on 11/02/2021

Database	#
Ovid Embase	1390
Ovid Medline	732
Ovid Emcare	171
Ovid Cochrane (CDSR & CENTRAL)	425
EBSCO CINAHL	133
Scopus	617
Web of Science	1968
Clinicaltrials.gov	76
ISRCTN	7
Total	5519
Duplicates removed	2428
Results to screen	3091

Database(s): **Embase** 1974 to 2021 February 09

Search Strategy:

#	Searches	Results
1	imatinib/	42960
2	imatinib.ti,ab,kw.	24383
3	gleevec.ti,ab,kw.	1370
4	dasatinib/	14060
5	dasatinib.ti,ab,kw.	7621
6	sprycel.ti,ab,kw.	126
7	nilotinib/	9092
8	nilotinib.ti,ab,kw.	5301
9	tasigna.ti,ab,kw.	111
10	bosutinib/	2595
11	bosutinib.ti,ab,kw.	1157
12	ponatinib/	2906
13	ponatinib.ti,ab,kw.	1634
14	ibrutinib/	7131
15	ibrutinib.ti,ab,kw.	5306
16	lestaurtinib/	822
17	lestaurtinib.ti,ab,kw.	185
18	quizartinib/	1002
19	quizartinib.ti,ab,kw.	437
20	crenolanib/	497
21	crenolanib.ti,ab,kw.	210
22	pinometostat/	151
23	pinometostat.ti,ab,kw.	20
24	sorafenib/	30329
25	sorafenib.ti,ab,kw.	16819
26	sunitinib/	23357
27	sunitinib.ti,ab,kw.	11498
28	midostaurin/	2478
29	midostaurin.ti,ab,kw.	786
30	lintuzumab/	157
31	lintuzumab.ti,ab,kw.	69

32	gemtuzumab/	443
33	gemtuzumab.ti,ab,kw.	1214
34	blinatumomab/	1842
35	blinatumomab.ti,ab,kw.	1083
36	inotuzumab/	482
37	inotuzumab.ti,ab,kw.	555
38	gilteritinib/	461
39	gilteritinib.ti,ab,kw.	249
40	vincristine/	102392
41	Vincristine.ti,ab,kw.	26657
42	daunorubicin/	28555
43	cytarabine plus daunorubicin/	561
44	daunorubicin.ti,ab,kw.	7503
45	daunomycin.ti,ab,kw.	1943
46	Inotuzumab Ozogamicin/	1066
47	ozogamicin.ti,ab,kw.	1514
48	cytarabine/	62070
49	Cytarabine.ti,ab,kw.	13018
50	cytosine arabinoside.ti,ab,kw.	5608
51	ara-C.ti,ab,kw.	6834
52	doxorubicin/	194206
53	cyclophosphamide plus doxorubicin plus prednisolone plus rituximab plus vincristine/	2930
54	cyclophosphamide plus doxorubicin plus etoposide plus prednisolone plus vincristine/	171
55	cyclophosphamide plus doxorubicin plus etoposide plus prednisolone plus rituximab plus vincristine/	393
56	doxorubicin.ti,ab,kw.	63301
57	Adriamycin.ti,ab,kw.	20295
58	idarubicin/	10935
59	idarubicin.ti,ab,kw.	3056
60	asparaginase macrogol/	1620
61	L-asparaginase.ti,ab,kw.	3774
62	PEG-L-asparaginase.ti,ab,kw.	46
63	pegaspargase.ti,ab,kw.	301
64	etoposide/	89596
65	Etoposide.ti,ab,kw.	30349
66	mercaptopurine/	25573
67	6-mercaptopurine.ti,ab,kw.	4918
68	"6-MP".ti,ab,kw.	1890
69	tioguanine/	9331
70	6-thioguanine.ti,ab,kw.	3063
71	"6-TG".ti,ab,kw.	815
72	methotrexate/	181679
73	Methotrexate.ti,ab,kw.	70315
74	mitoxantrone/	23782
75	Mitoxantrone.ti,ab,kw.	7422
76	cyclophosphamide/	220062
77	Cyclophosphamide.ti,ab,kw.	77266
78	prednisone/	174300
79	prednisone.ti,ab,kw.	49947
80	prednisolone/	127791
81	prednisolone.ti,ab,kw.	40064
82	dexamethasone/	154292
83	dexamethasone.ti,ab,kw.	80371
84	hydrocortisone/	127619
85	hydrocortisone.ti,ab,kw.	19658
86	or/1-86	1072884

87	exp Leukemia/	310865
88	cancer*.ti,ab,kw.	2676340
89	neoplas*.ti,ab,kw.	448060
90	leukemia*1.ti,ab,kw.	305209
91	leukaemia*1.ti,ab,kw.	48326
92	metasta*.ti,ab,kw.	771663
93	malignan*.ti,ab,kw.	835996
94	myeloma*.ti,ab,kw.	85853
95	oncolog*.ti,ab,kw.	305985
96	or/88-96	3981811
97	personalized medicine/	48484
98	((precision or personal*) adj2 dos*).ti,ab,kw.	3514
99	drug monitoring/	54577
100	((Therapeutic or drug*) adj2 monitor*).ti,ab,kw.	32209
101	TDM.ti,ab,kw.	5954
102	TDMx.ti,ab,kw.	10
103	InsightRx.ti,ab,kw.	7
104	DoseMe.ti,ab,kw.	9
105	(individual* adj2 dos*).ti,ab,kw.	10967
106	plasma concentration.ti,ab,kw.	48265
107	plasma level*.ti,ab,kw.	104247
108	toxicity guided dos*.ti,ab,kw.	12
109	toxicity adjust* dos*.ti,ab,kw.	16
110	"TAD".ti,ab,kw.	2786
111	optimal dos*.ti,ab,kw.	18842
112	optimi?ed dos*.ti,ab,kw.	1036
113	model informed dos*.ti,ab,kw.	27
114	MIPD.ti,ab,kw.	140
115	trough concentration.ti,ab,kw.	2572
116	(pharmacokinetic* adj2 (physiological based or population)).ti,ab,kw.	8990
117	POP PK.ti,ab,kw.	138
118	POPPK.ti,ab,kw.	656
119	PBPK.ti,ab,kw.	3835
120	or/98-120	309700
121	exp adolescence/	82014
122	exp adolescent/	1569687
123	exp child/	2704713
124	girl/	40271
125	boy/	27501
126	adolescen*.ti,ab,kw.	392586
127	baby.ti,ab,kw.	55706
128	babies.ti,ab,kw.	53432
129	boy*1.ti,ab,kw.	199735
130	boyhood.ti,ab,kw.	94
131	child*.ti,ab,kw.	1818404
132	girl*1.ti,ab,kw.	203724
133	juvenil*.ti,ab,kw.	102962
134	kid*1.ti,ab,kw.	13324
135	minor*1.ti,ab,kw.	299615
136	neonat*.ti,ab,kw.	362755
137	newborn*.ti,ab,kw.	201012
138	new-born.ti,ab,kw.	5099
139	paediatric*.ti,ab,kw.	122576
140	pediatric*.ti,ab,kw.	489028
141	peadiatric*.ti,ab,kw.	239
142	perinat*.ti,ab,kw.	107100
143	puber*.ti,ab,kw.	53967

144	pubescen*.ti,ab,kw.	2857
145	preschool*.ti,ab,kw.	36413
146	kindergart*.ti,ab,kw.	7978
147	school*.ti,ab,kw.	360928
148	teen*.ti,ab,kw.	43612
149	toddler*.ti,ab,kw.	15464
150	underage*.ti,ab,kw.	1672
151	under-age*.ti,ab,kw.	6708
152	youth*.ti,ab,kw.	99682
153	or/122-153	4771976
154	and/87,97,121,154	1390

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 09, 2021

Search Strategy:

#	Searches	Results
1	Imatinib Mesylate/	10409
2	imatinib.ti,ab,kf.	13898
3	gleevec.ti,ab,kf,nm.	987
4	Dasatinib/	2147
5	dasatinib.ti,ab,kf,nm.	3806
6	sprycel.ti,ab,kf,nm.	52
7	nilotinib.ti,ab,kf,nm.	2147
8	tasigna.ti,ab,kf,nm.	49
9	bosutinib.ti,ab,kf,nm.	562
10	ponatinib.ti,ab,kf,nm.	751
11	ibrutinib.ti,ab,kf,nm.	2334
12	lestaurtinib.ti,ab,kf,nm.	155
13	quizartinib.ti,ab,kf,nm.	202
14	crenolanib.ti,ab,kf,nm.	90
15	pinometostat.ti,ab,kf,nm.	10
16	sorafenib/	5001
17	sorafenib.ti,ab,kf.	8855
18	sunitinib/	3645
19	sunitinib.ti,ab,kf.	5933
20	midostaurin.ti,ab,kf,nm.	602
21	lintuzumab.ti,ab,kf,nm.	36
22	gemtuzumab/	525
23	gemtuzumab.ti,ab,kf.	672

24	blinatumomab.ti,ab,kf,nm.	531
25	inotuzumab.ti,ab,kf,nm.	287
26	gilteritinib.ti,ab,kf,nm.	143
27	Vincristine/	23455
28	vincristine.ti,ab,kf,nm.	31982
29	Daunorubicin/	7932
30	daunorubicin.ti,ab,kf,nm.	10045
31	daunomycin.ti,ab,kf,nm.	1886
32	Inotuzumab Ozogamicin/	124
33	ozogamicin.ti,ab,kf.	825
34	Cytarabine/	14755
35	cytarabine.ti,ab,kf,nm.	17771
36	cytosine arabinoside.ti,ab,kf,nm.	4893
37	ara-C.ti,ab,kf,nm.	4618
38	Doxorubicin/	53812
39	doxorubicin.ti,ab,kf,nm.	71531
40	Adriamycin.ti,ab,kf,nm.	16010
41	Idarubicin/	1710
42	idarubicin.ti,ab,kf,nm.	2332
43	L-asparaginase.ti,ab,kf,nm.	3071
44	PEG-L-asparaginase.ti,ab,kf,nm.	25
45	Asparaginase/	4609
46	pegaspargase.ti,ab,kf,nm.	340
47	Etoposide/	16851
48	etoposide.ti,ab,kf,nm.	25992
49	Mercaptopurine/	6288
50	6-mercaptopurine.ti,ab,kf,nm.	3788
51	"6-MP".ti,ab,kf,nm.	1109
52	Thioguanine/	2584
53	6-thioguanine.ti,ab,kf,nm.	2520
54	"6-TG".ti,ab,kf,nm.	519
55	Methotrexate/	38412
56	methotrexate.ti,ab,kf,nm.	55637
57	Mitoxantrone/	4284

58	mitoxantrone.ti,ab,kf,nm.	6339
59	Cyclophosphamide/	50418
60	cyclophosphamide.ti,ab,kf,nm.	71736
61	Prednisone/	39744
62	prednisone.ti,ab,kf,nm.	54271
63	Prednisolone/	33116
64	prednisolone.ti,ab,kf,nm.	46906
65	Dexamethasone/	51962
66	dexamethasone.ti,ab,kf,nm.	73580
67	Hydrocortisone/	72676
68	hydrocortisone.ti,ab,kf,nm.	78206
69	or/1-69	469724
70	exp Leukemia/	235182
71	cancer*.ti,ab,kf.	1896549
72	neoplas*.ti,ab,kf.	410784
73	leukemia*1.ti,ab,kf.	230003
74	leukaemia*1.ti,ab,kf.	37396
75	metasta*.ti,ab,kf.	535008
76	malignan*.ti,ab,kf.	598362
77	myeloma*.ti,ab,kf.	56254
78	oncolog*.ti,ab,kf.	167371
79	or/71-79	2983530
80	Precision Medicine/	19372
81	((precision or personal*) adj2 dos*).ti,ab,kf.	2290
82	Drug Monitoring/	21496
83	((Therapeutic or drug*) adj2 monitor*).ti,ab,kf.	20759
84	TDM.ti,ab,kf.	3352
85	TDMx.ti,ab,kf.	7
86	InsightRx.ti,ab,kf.	5
87	DoseMe.ti,ab,kf.	4
88	(individual* adj2 dos*).ti,ab,kf.	7147
89	plasma concentration.ti,ab,kf.	37339
90	plasma level*.ti,ab,kf.	77307
91	toxicity guided dos*.ti,ab,kf.	8

92	toxicity adjust* dos*.ti,ab,kf.	7
93	"TAD".ti,ab,kf.	1987
94	optimal dos*.ti,ab,kf.	12698
95	optimi* dos*.ti,ab,kf.	1342
96	model informed dos*.ti,ab,kf.	18
97	MIPD.ti,ab,kf.	88
98	trough concentration.ti,ab,kf.	1595
99	(pharmacokinetic* adj2 (physiological based or population)).ti,ab,kf.	6195
100	POP PK.ti,ab,kf.	35
101	POPPK.ti,ab,kf.	261
102	PBPK.ti,ab,kf.	2649
103	or/81-103	196503
104	exp Adolescent/	2067391
105	exp Child/	1944611
106	adolescen*.ti,ab,kf.	313307
107	baby.ti,ab,kf.	39694
108	babies.ti,ab,kf.	38034
109	boy*1.ti,ab,kf.	149723
110	boyhood.ti,ab,kf.	86
111	child*.ti,ab,kf.	1480254
112	girl*1.ti,ab,kf.	153116
113	juvenil*.ti,ab,kf.	85948
114	kid*1.ti,ab,kf.	9124
115	minor*1.ti,ab,kf.	234252
116	neonat*.ti,ab,kf.	278633
117	newborn*.ti,ab,kf.	180886
118	new-born.ti,ab,kf.	4087
119	paediatric*.ti,ab,kf.	71428
120	pediatric*.ti,ab,kf.	320168
121	peadiatric*.ti,ab,kf.	59
122	perinat*.ti,ab,kf.	79328
123	puber*.ti,ab,kf.	40356
124	pubescen*.ti,ab,kf.	2480
125	preschool*.ti,ab,kf.	30549

126	kindergart*.ti,ab,kf.	7060
127	school*.ti,ab,kf.	296755
128	teen*.ti,ab,kf.	31757
129	toddler*.ti,ab,kf.	11870
130	underage*.ti,ab,kf.	1316
131	under-age*.ti,ab,kf.	5053
132	youth*.ti,ab,kf.	85408
133	or/105-133	4439277
134	and/70,80,104,134	732

Database(s): **Ovid Emcare** 1995 to 2021 Week 05

Search Strategy:

#	Searches	Results
1	imatinib/	6325
2	imatinib.ti,ab,kw.	2562
3	gleevec.ti,ab,kw.	149
4	dasatinib/	2016
5	dasatinib.ti,ab,kw.	674
6	sprycel.ti,ab,kw.	13
7	nilotinib/	1326
8	nilotinib.ti,ab,kw.	501
9	tasigna.ti,ab,kw.	16
10	bosutinib/	374
11	bosutinib.ti,ab,kw.	92
12	ponatinib/	452
13	ponatinib.ti,ab,kw.	143
14	ibrutinib/	978
15	ibrutinib.ti,ab,kw.	482
16	lestaurtinib/	145
17	lestaurtinib.ti,ab,kw.	21
18	quizartinib/	89
19	quizartinib.ti,ab,kw.	25
20	crenolanib/	60
21	crenolanib.ti,ab,kw.	9

22	pinometostat/	18
23	pinometostat.ti,ab,kw.	2
24	sorafenib/	5033
25	sorafenib.ti,ab,kw.	1930
26	sunitinib/	4153
27	sunitinib.ti,ab,kw.	1394
28	midostaurin/	287
29	midostaurin.ti,ab,kw.	88
30	lintuzumab/	17
31	lintuzumab.ti,ab,kw.	7
32	gemtuzumab/	61
33	gemtuzumab.ti,ab,kw.	131
34	blinatumomab/	296
35	blinatumomab.ti,ab,kw.	114
36	inotuzumab/	163
37	inotuzumab.ti,ab,kw.	63
38	gilteritinib/	64
39	gilteritinib.ti,ab,kw.	32
40	vincristine/	14240
41	Vincristine.ti,ab,kw.	2551
42	daunorubicin/	2696
43	cytarabine plus daunorubicin/	64
44	daunorubicin.ti,ab,kw.	481
45	daunomycin.ti,ab,kw.	40
46	Inotuzumab Ozogamicin/	163
47	ozogamicin.ti,ab,kw.	165
48	cytarabine/	6685
49	Cytarabine.ti,ab,kw.	1116
50	cytosine arabinoside.ti,ab,kw.	148
51	ara-C.ti,ab,kw.	260
52	doxorubicin/	28644
53	cyclophosphamide plus doxorubicin plus prednisolone plus rituximab plus vincristine/	429
54	cyclophosphamide plus doxorubicin plus etoposide plus prednisolone plus vincristine/	26

55	cyclophosphamide plus doxorubicin plus etoposide plus prednisolone plus rituximab plus vincristine/	71
56	doxorubicin.ti,ab,kw.	7488
57	Adriamycin.ti,ab,kw.	1040
58	idarubicin/	1369
59	idarubicin.ti,ab,kw.	188
60	asparaginase macrogol/	252
61	L-asparaginase.ti,ab,kw.	222
62	PEG-L-asparaginase.ti,ab,kw.	3
63	pegaspargase.ti,ab,kw.	49
64	etoposide/	13885
65	Etoposide.ti,ab,kw.	2898
66	mercaptopurine/	2932
67	6-mercaptopurine.ti,ab,kw.	296
68	"6-MP".ti,ab,kw.	109
69	tioguanine/	679
70	6-thioguanine.ti,ab,kw.	123
71	"6-TG".ti,ab,kw.	52
72	methotrexate/	29325
73	Methotrexate.ti,ab,kw.	7672
74	mitoxantrone/	3555
75	Mitoxantrone.ti,ab,kw.	648
76	cyclophosphamide/	32776
77	Cyclophosphamide.ti,ab,kw.	7020
78	prednisone/	29262
79	prednisone.ti,ab,kw.	4568
80	prednisolone/	18002
81	prednisolone.ti,ab,kw.	3322
82	dexamethasone/	25863
83	dexamethasone.ti,ab,kw.	8356
84	hydrocortisone/	21530
85	hydrocortisone.ti,ab,kw.	1676
86	or/1-86	154768
87	exp Leukemia/	30411

88	cancer*.ti,ab,kw.	442888
89	neoplas*.ti,ab,kw.	54694
90	leukemia*1.ti,ab,kw.	22078
91	leukaemia*1.ti,ab,kw.	4060
92	metasta*.ti,ab,kw.	103397
93	malignan*.ti,ab,kw.	112432
94	myeloma*.ti,ab,kw.	8080
95	oncolog*.ti,ab,kw.	72000
96	or/88-96	601324
97	personalized medicine/	11564
98	((precision or personal*) adj2 dos*).ti,ab,kw.	1056
99	drug monitoring/	9543
100	((Therapeutic or drug*) adj2 monitor*).ti,ab,kw.	4580
101	TDM.ti,ab,kw.	572
102	TDMx.ti,ab,kw.	1
103	InsightRx.ti,ab,kw.	0
104	DoseMe.ti,ab,kw.	0
105	(individual* adj2 dos*).ti,ab,kw.	1751
106	plasma concentration.ti,ab,kw.	5367
107	plasma level*.ti,ab,kw.	12339
108	toxicity guided dos*.ti,ab,kw.	3
109	toxicity adjust* dos*.ti,ab,kw.	4
110	"TAD".ti,ab,kw.	427
111	optimal dos*.ti,ab,kw.	3238
112	optimi?ed dos*.ti,ab,kw.	141
113	model informed dos*.ti,ab,kw.	1
114	MIPD.ti,ab,kw.	18
115	trough concentration.ti,ab,kw.	280
116	(pharmacokinetic* adj2 (physiological based or population)).ti,ab,kw.	1282
117	POP PK.ti,ab,kw.	7
118	POPPK.ti,ab,kw.	38
119	PBPK.ti,ab,kw.	205
120	or/98-120	48374
121	exp adolescence/	36613

122	exp adolescent/	360220
123	exp child/	679766
124	girl/	32705
125	boy/	27239
126	adolescen*.ti,ab,kw.	164516
127	baby.ti,ab,kw.	16255
128	babies.ti,ab,kw.	13647
129	boy*1.ti,ab,kw.	55321
130	boyhood.ti,ab,kw.	46
131	child*.ti,ab,kw.	544584
132	girl*1.ti,ab,kw.	60286
133	juvenil*.ti,ab,kw.	15617
134	kid*1.ti,ab,kw.	4151
135	minor*1.ti,ab,kw.	50830
136	neonat*.ti,ab,kw.	81590
137	newborn*.ti,ab,kw.	40342
138	new-born.ti,ab,kw.	679
139	paediatric*.ti,ab,kw.	34927
140	pediatric*.ti,ab,kw.	133466
141	peadiatric*.ti,ab,kw.	28
142	perinat*.ti,ab,kw.	27508
143	puber*.ti,ab,kw.	8461
144	pubescen*.ti,ab,kw.	452
145	preschool*.ti,ab,kw.	18281
146	kindergart*.ti,ab,kw.	4726
147	school*.ti,ab,kw.	163652
148	teen*.ti,ab,kw.	17054
149	toddler*.ti,ab,kw.	7214
150	underage*.ti,ab,kw.	1079
151	under-age*.ti,ab,kw.	1736
152	youth*.ti,ab,kw.	61358
153	or/122-153	1176622
154	and/87,97,121,154	171

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** January 2021**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to February 10, 2021
Search Strategy:

#	Searches	Results
1	Imatinib Mesylate/	420
2	imatinib.ti,ab,kw.	1551
3	gleevec.ti,ab,kw.	87
4	Dasatinib/	109
5	dasatinib.ti,ab,kw.	490
6	sprycel.ti,ab,kw.	46
7	nilotinib.ti,ab,kw.	433
8	tasigna.ti,ab,kw.	34
9	bosutinib.ti,ab,kw.	136
10	ponatinib.ti,ab,kw.	93
11	ibrutinib.ti,ab,kw.	587
12	lestaurtinib.ti,ab,kw.	15
13	quizartinib.ti,ab,kw.	66
14	crenolanib.ti,ab,kw.	27
15	pinometostat.ti,ab,kw.	3
16	sorafenib/	482
17	sorafenib.ti,ab,kw.	1954
18	sunitinib/	317
19	sunitinib.ti,ab,kw.	1262
20	midostaurin.ti,ab,kw.	97
21	lintuzumab.ti,ab,kw.	11
22	gemtuzumab/	65
23	gemtuzumab.ti,ab,kw.	202
24	blinatumomab.ti,ab,kw.	87
25	inotuzumab.ti,ab,kw.	109
26	gilteritinib.ti,ab,kw.	50
27	Vincristine/	2349
28	vincristine.ti,ab,kw.	3367
29	Daunorubicin/	631

30	daunorubicin.ti,ab,kw.	964
31	daunomycin.ti,ab,kw.	66
32	Inotuzumab Ozogamicin/	18
33	ozogamicin.ti,ab,kw.	286
34	Cytarabine/	1342
35	cytarabine.ti,ab,kw.	2166
36	cytosine arabinoside.ti,ab,kw.	454
37	ara-C.ti,ab,kw.	755
38	Doxorubicin/	3828
39	doxorubicin.ti,ab,kw.	6114
40	Adriamycin.ti,ab,kw.	1823
41	Idarubicin/	249
42	idarubicin.ti,ab,kw.	599
43	L-asparaginase.ti,ab,kw.	280
44	PEG-L-asparaginase.ti,ab,kw.	10
45	Asparaginase/	333
46	pegaspargase.ti,ab,kw.	91
47	Etoposide/	1786
48	etoposide.ti,ab,kw.	3515
49	Mercaptopurine/	263
50	6-mercaptopurine.ti,ab,kw.	425
51	"6-MP".ti,ab,kw.	196
52	Thioguanine/	223
53	6-thioguanine.ti,ab,kw.	148
54	"6-TG".ti,ab,kw.	23
55	Methotrexate/	4144
56	methotrexate.ti,ab,kw.	10815
57	Mitoxantrone/	513
58	mitoxantrone.ti,ab,kw.	1237
59	Cyclophosphamide/	5104
60	cyclophosphamide.ti,ab,kw.	10605
61	Prednisone/	3991
62	prednisone.ti,ab,kw.	8040
63	Prednisolone/	3000

64	prednisolone.ti,ab,kw.	5738
65	Dexamethasone/	4538
66	dexamethasone.ti,ab,kw.	11189
67	Hydrocortisone/	5956
68	hydrocortisone.ti,ab,kw.	4462
69	or/1-69	66038
70	exp Leukemia/	4767
71	cancer*.ti,ab,kw.	176578
72	neoplas*.ti,ab,kw.	21957
73	leukemia*1.ti,ab,kw.	13248
74	leukaemia*1.ti,ab,kw.	2202
75	metasta*.ti,ab,kw.	44556
76	malignan*.ti,ab,kw.	29247
77	myeloma*.ti,ab,kw.	5782
78	oncolog*.ti,ab,kw.	29094
79	or/71-79	216189
80	Precision Medicine/	474
81	((precision or personal*) adj2 dos*).ti,ab,kw.	237
82	Drug Monitoring/	1823
83	((Therapeutic or drug*) adj2 monitor*).ti,ab,kw.	3034
84	TDM.ti,ab,kw.	328
85	TDMx.ti,ab,kw.	2
86	InsightRx.ti,ab,kw.	1
87	DoseMe.ti,ab,kw.	0
88	(individual* adj2 dos*).ti,ab,kw.	2567
89	plasma concentration.ti,ab,kw.	13567
90	plasma level*.ti,ab,kw.	11931
91	toxicity guided dos*.ti,ab,kw.	0
92	toxicity adjust* dos*.ti,ab,kw.	7
93	"TAD".ti,ab,kw.	199
94	optimal dos*.ti,ab,kw.	4329
95	optimi* dos*.ti,ab,kw.	523
96	model informed dos*.ti,ab,kw.	1
97	MIPD.ti,ab,kw.	11

98	trough concentration.ti,ab,kw.	638
99	(pharmacokinetic* adj2 (physiological based or population)).ti,ab,kw.	2262
100	POP PK.ti,ab,kw.	32
101	POPPK.ti,ab,kw.	111
102	PBPK.ti,ab,kw.	84
103	or/81-103	38734
104	exp Adolescent/	106011
105	exp Child/	56354
106	adolescen*.ti,ab,kw.	53456
107	baby.ti,ab,kw.	4653
108	babies.ti,ab,kw.	4733
109	boy*1.ti,ab,kw.	7274
110	boyhood.ti,ab,kw.	0
111	child*.ti,ab,kw.	152223
112	girl*1.ti,ab,kw.	7939
113	juvenil*.ti,ab,kw.	3908
114	kid*1.ti,ab,kw.	1167
115	minor*1.ti,ab,kw.	17577
116	neonat*.ti,ab,kw.	23596
117	newborn*.ti,ab,kw.	16219
118	new-born.ti,ab,kw.	203
119	paediatric*.ti,ab,kw.	7839
120	pediatric*.ti,ab,kw.	30494
121	peadiatric*.ti,ab,kw.	20
122	perinat*.ti,ab,kw.	6396
123	puber*.ti,ab,kw.	1843
124	pubescen*.ti,ab,kw.	63
125	preschool*.ti,ab,kw.	11869
126	kindergart*.ti,ab,kw.	770
127	school*.ti,ab,kw.	35093
128	teen*.ti,ab,kw.	2893
129	toddler*.ti,ab,kw.	1864
130	underage*.ti,ab,kw.	201
131	under-age*.ti,ab,kw.	469839

132	youth*.ti,ab,kw.	7998
133	or/105-133	664617
134	and/70,80,104,134	425

CINAHL – EBSCO

#	Query	Limiters/Expanders	Results
S1	(MH "Imatinib")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	861
S2	TI imatinib OR AB imatinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,578
S3	TI gleevec OR AB gleevec	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	113
S4	(MH "Dasatinib")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	117
S5	TI Dasatinib OR AB Dasatinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	765
S6	TI sprycel OR AB sprycel	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	13
S7	(MH "Nilotinib")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	90
S8	TI nilotinib OR AB nilotinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	564
S9	TI tasigna OR AB tasigna	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	22
S10	(MH "Vincristine")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,345
S11	TI Vincristine OR AB Vincristine	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,129
S12	(MH "Imatinib")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	861
S13	TI bosutinib OR AB bosutinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	117
S14	TI ponatinib OR AB ponatinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	170
S15	TI ibrutinib OR AB ibrutinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	670
S16	TI lestaurtinib OR AB lestaurtinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	13

S17	TI quizartinib OR AB quizartinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	21
S18	TI pinometostat OR AB pinometostat	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2
S19	(MH "Sorafenib")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	895
S20	TI sorafenib OR AB sorafenib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,042
S21	(MH "Sunitinib")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	87
S22	TI sunitinib OR AB sunitinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,786
S23	TI midostaurin OR AB midostaurin	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	83
S24	TI lintuzumab OR AB lintuzumab	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	9
S25	TI gemtuzumab OR AB gemtuzumab	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	148
S26	TI blinatumomab OR AB blinatumomab	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	148
S27	(MH "Inotuzumab Ozogamicin")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2
S28	TI inotuzumab OR AB inotuzumab	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	79
S29	TI ozogamicin OR AB ozogamicin	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	205
S30	TI gilteritinib OR AB gilteritinib	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	40
S31	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	11,342
S32	(MH "Leukemia+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	22,717
S33	TI cancer* OR AB cancer*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	409,890
S34	TI neoplas* OR AB neoplas*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	26,952
S35	TI leukemia OR AB leukemia	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	23,402

S36	TI leukemias OR AB leukemias	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	17,781
S37	TI leukaemia OR AB leukaemia	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	18,740
S38	TI leukaemias OR AB leukaemias	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	17,700
S39	TI metasta* OR AB metasta*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	75,501
S40	TI malignan* OR AB malignan*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	73,542
S41	TI myeloma* OR AB myeloma*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	8,409
S42	TI oncolog* OR AB oncolog*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	57,923
S43	S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	539,675
S44	(MH "Individualized Medicine")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,414
S45	TI (individual* N2 dos*) OR AB (individual* N2 dos*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,587
S46	TI (((precision or personal*) N2 dos*)) OR AB (((precision or personal*) N2 dos*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	353
S47	(MH "Drug Monitoring")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	8,012
S48	TI (((Therapeutic or drug*) N2 monitor*)) OR AB (((Therapeutic or drug*) N2 monitor*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	4,229
S49	TI TDM OR AB TDM	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	590
S50	TI InsightRx OR AB InsightRx	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2
S51	TI DoseMe OR AB DoseMe	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2
S52	TI "plasma concentration" OR AB "plasma concentration"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,788
S53	TI "plasma level*" OR AB "plasma level*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	7,692
S54	TI TDMx OR AB TDMx	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1
S55	TI "toxicity guided dos*" OR AB "toxicity guided dos*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5

S56	TI "toxicity adjust* dos*" OR AB "toxicity adjust* dos*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5
S57	TI "TAD" OR AB "TAD"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	216
S58	TI "optimal dos*" OR AB "optimal dos*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,329
S59	TI "optimi* dos*" OR AB "optimi* dos*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	261
S60	TI "model informed dos*" OR AB "model informed dos*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	4
S61	TI MIPD OR AB MIPD	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	19
S62	TI "trough concentration" OR AB "trough concentration"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	311
S63	TI ((pharmacokinetic* N2 ("physiological based " OR population))) OR AB ((pharmacokinetic* N2 (physiological based or population)))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,629
S64	TI "POP PK" OR AB "POP PK"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	7
S65	TI POPPK OR AB POPPK	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	59
S66	TI PBPK OR AB PBPK	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	171
S67	S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	33,466
S68	(MH "Adolescence+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	544,027
S69	(MH "Child+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	688,728
S70	TI adolescen* OR AB adolescen*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	139,418
S71	TI baby OR AB baby	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	30,968
S72	TI babies OR AB babies	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	27,884
S73	TI (boy OR boys) OR AB (boy OR boys)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	39,321

S74	TI boyhood OR AB boyhood	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	33
S75	TI child* OR AB child*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	505,865
S76	TI (girl OR girls) OR AB (girl OR girls)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	43,805
S77	TI juvenil* OR AB juvenil*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	10,512
S78	TI (kid OR kids) OR AB (kid OR kids)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	10,338
S79	TI (minor OR minors) OR AB (minor OR minors)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	31,600
S80	TI neonat* OR AB neonat*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	69,750
S81	TI newborn* OR AB newborn*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	31,963
S82	TI "new-born" OR AB "new-born"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	387
S83	TI paediatric* OR AB paediatric*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	26,533
S84	TI pediatric* OR AB pediatric*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	117,530
S85	TI perinat* OR AB perinat*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	24,959
S86	TI peadiatric* OR AB peadiatric*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	17
S87	TI puber* OR AB puber*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	6,146
S88	pubescen* OR AB pubescen*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	290
S89	TI preschool* OR AB preschool*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	13,881
S90	TI kindergart* OR AB kindergart*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,059
S91	TI school* OR AB school*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	147,999
S92	TI teen* OR AB teen*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	19,451
S93	TI toddler* OR AB toddler*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	6,808

S94	TI underage* OR AB underage*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	880
S95	TI "under-age*" OR AB "under-age*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,408
S96	TI youth* OR AB youth*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	51,993
S97	S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,350,400
S98	MH "Daunorubicin")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	253
S99	TI Daunorubicin OR AB Daunorubicin	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	327
S100	(MH "Cytarabine")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,136
S101	TI Cytarabine OR AB Cytarabine	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,064
S102	TI "cytosine arabinoside" OR AB "cytosine arabinoside"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	109
S103	TI "ara-C" OR AB "ara-C"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	160
S104	(MH "Doxorubicin")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,159
S105	TI Doxorubicin OR AB Doxorubicin	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	4,783
S106	TI Adriamycin OR AB Adriamycin	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	619
S107	(MH "Idarubicin")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	132
S108	TI Idarubicin OR TI Idarubicin	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	81
S109	(MH "Asparaginase")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	403
S110	TI "L-asparaginase" OR AB "L-asparaginase"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	183
S111	TI "PEG-L-asparaginase" OR AB "PEG-L-asparaginase"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2
S112	TI pegaspargase OR AB pegaspargase	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	67

S113	(MH "Etoposide")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,734
S114	TI Etoposide OR AB Etoposide	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,078
S115	TI "6-mercaptopurine" OR AB "6-mercaptopurine"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	223
S116	TI "6-MP" OR AB "6-MP"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	71
S117	TI "6-thioguanine" OR AB "6-thioguanine"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	90
S118	TI "6-TG" OR AB "6-TG"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	10
S119	(MH "Methotrexate")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	6,149
S120	TI Methotrexate OR AB Methotrexate	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	6,630
S121	(MH "Mitoxantrone")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	446
S122	TI Mitoxantrone OR AB Mitoxantrone	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	461
S123	(MH "Cyclophosphamide")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,287
S124	TI Cyclophosphamide OR AB Cyclophosphamide	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,816
S125	(MH "Prednisone")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,026
S126	TI Prednisone OR AB Prednisone	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	4,003
S127	(MH "Prednisolone")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,406
S128	TI Prednisolone OR AB Prednisolone	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,871
S129	(MH "Dexamethasone")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	5,905
S130	TI Dexamethasone OR AB Dexamethasone	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	6,489
S131	(MH "Hydrocortisone")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	8,754
S132	TI hydrocortisone OR AB Hydrocortisone	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,217

S133	S32 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113 OR S114 OR S115 OR S116 OR S117 OR S118 OR S119 OR S120 OR S121 OR S122 OR S123 OR S124 OR S125 OR S126 OR S127 OR S128 OR S129 OR S130 OR S131 OR S132 OR S133	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	58,101
S134	S44 AND S68 AND S98 AND S134	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	133

Web of Science

# 1	617	**TOPIC:** ((imatinib OR gleevec OR Dasatinib OR sprycel OR nilotinib OR tasigna OR Vincristine OR bosutinib OR ponatinib OR ibrutinib OR lestaurtinib OR quizartinib OR crenolanib OR pinometostat OR sorafenib OR sunitinib OR midostaurin OR lintuzumab OR gilteritinib OR tisagenlecleucel OR gemtuzumab ozogamicin OR blinatumomab OR inotuzumab OR Daunorubicin OR daunomycin OR Cytarabine OR "cytosine arabinoside" OR "ara-C" OR Doxorubicin OR Adriamycin OR Idarubicin OR "L-asparaginase" OR "PEG-L-asparaginase" OR pegaspargase OR Etoposide OR "6-mercaptopurine" OR "6-MP" OR "6-thioguanine" OR "6-TG" OR Methotrexate OR Mitoxantrone OR Cyclophosphamide OR Prednisone OR Prednisolone OR Dexamethasone OR hydrocortisone) AND (cancer* OR neoplas* OR leukemia OR leukemias OR leukaemia OR leukaemias OR metasta* OR malignan* OR myeloma* OR oncolog*) AND ((individual* NEAR/2 dos*) OR ((precision or personal*) NEAR/2 dos*) OR ((Therapeutic or drug*) NEAR/2 monitor*) OR TDM OR TDMx OR InsightRx OR DoseMe OR "plasma concentration" OR "plasma level*" OR "toxicity guided dos*" OR "TAD" OR "toxicity adjust* dos*" OR "optimal dos*" OR "optimi* dos*" OR "model informed dos*" OR MIPD OR "trough concentration" OR (pharmacokinetic* NEAR/2 ("physiological based" OR population)) OR "POP PK" OR POPPK OR PBPK) AND (adolescen* OR baby OR babies OR boy OR boys OR boyhood OR child* OR girl OR girls OR juvenil* OR kid OR kids OR minor OR minors OR neonat* OR newborn* OR "new-born" OR paediatric* OR pediatric* OR perinat* OR puber* OR pubescen* OR preschool* OR kindergart* OR school* OR teen* OR toddler* OR underage* OR "under-age*" OR youth*)) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*

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paediatric* OR pediatric* OR perinat* OR puber* OR pubescen* OR preschool* OR kindergart* OR school* OR teen* OR toddler* OR underage* OR "under-age*" OR youth*)

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Applied Filters: ☑ **Child (birth–17)**

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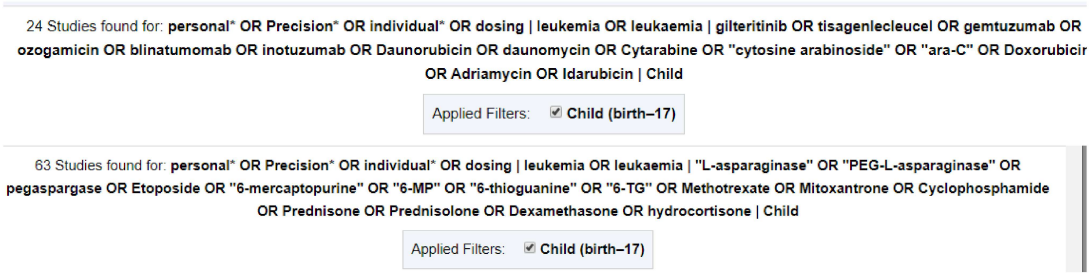

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ISRCTN registry (selected -

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