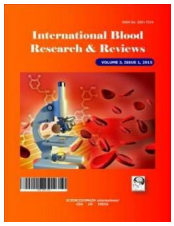

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Outpatient Management of Acute Leukemia: A Systematic Review and Meta Analysis

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Authors' contributions

This work was carried out in collaboration between all authors. Author OE designed study idea initiator, planned the scope of search, put the research question, pubmed search, study selection from pubmed and EMBASE, data extraction, wrote the introduction, participation of writing the results and writing of the discussion and reference sections. Author SE searched the EMBASE, data extraction, analysis and table design, meta-analysis, wrote most of the results section, participated in writing the discussion, revision and proof reading of the whole manuscript except for the references section, final revision of the manuscript. Author DA contributed in the design of the study, managed the literature search and the acquisition of data, wrote the methodological section, participated in drafting the article and gave approval of the final version of the manuscript. Author AS designed study idea initiator, helped in searching the databases and in revision of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background/Aim: Outpatient chemotherapy administration for solid tumors is a commonly accepted practice given its advantage of easy and safe drug administration, ability to value the patient's wish to avoid hospitalization and decreased expenses compared to inpatient care. However, this practice is not commonly extended to patients with acute leukemia. The aim of this study was to compile the evidence about outpatient and early discharge of acute leukemia patients

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and its effects on the outcome.
Methods: A systematic review was done using MEDLINE, EMBASE and Cochrane Library databases. Both retrospective and prospective cohort studies as well as clinical trials for acute leukemia were included.
Results: Twenty one studies were included in this systematic review: Ten retrospective studies, 10 prospective studies and one non-randomized phase 2 trial. Most of the included studies reported that outpatient chemotherapy is feasible, safe, and resulted in decreased hospitalization days.
Conclusion: Studies reporting on outpatient and early discharge of acute leukemia are largely observational and highly heterogeneous. A trend towards a reduced incidence of septicemia was observed with early discharge. The effect of other clinical outcome measures was unclear. Reporting on social and economic impact is suboptimal.

Keywords: Acute leukemia; outpatient management; early hospital discharge ambulatory care.

1. INTRODUCTION

As with other types of malignancy, leukemia incidence is increasing worldwide [1]. Treatment largely consists of induction chemotherapy followed by consolidation chemotherapy which both present with severe hematological complications leading to infection and bleeding [2]. Over the last few years, moving chemotherapy administration, to the outpatient setting has provided the advantage of easy and safe drug administration and decreased expenses compared to inpatient care, whilst valuing the patient's wish to avoid hospitalization [3]. Avoidance of delays in medical intervention increased focus on quality of life and health care costs; and the reduced risk of severe multidrug resistant nosocomial infections are attractive reasons for early discharge of patients to continue their treatment in an outpatient settings [4,5], Although many patients with cancer now receive chemotherapy as outpatients, most cancer treatment centers do not extend this practice to patients with acute leukemia. This unwillingness primarily reflects the tendency of acute leukemia treatment regimens to exacerbate patients' preexisting neutropenia, leading to potentially life-threatening infections. Treatment also causes significantly reduced platelet counts with a significant risk of bleeding. Several investigations have demonstrated the feasibility of outpatient management of acute myeloid leukemia (AML) [6-8]. These studies have also shown that selective discharge of AML patients who have no complicating medical conditions is a low-risk practice that may reduce the incidence of resistant hospital-acquired infections [9,10,11].

1.1 Definitions of Outpatient Treatment and Early Discharge

Outpatients received their entire chemotherapy on an ambulatory basis while early discharge patients received their chemotherapy as inpatients and were discharged immediately after chemotherapy completion to be followed on an ambulatory basis through their neutropenic phase.

The aim of the current systematic review (SR) was to investigate the evidence surrounding the safety of discharge of acute leukemia patients and to measure the effect of early discharge on patient outcome.

2. MATERIALS AND METHODS

2.1 Inclusion Criteria

All studies reporting on early discharge of acute leukemia patients regardless of the type of acute leukemia were eligible for inclusion. All study design types were eligible, including and excluding group comparisons, except for case reports. Studies that did not report any outcomes were excluded.

2.2 Exclusion Criteria

Articles were excluded if they were duplicates of another study, were dissertation, a case report, a commentary, testing modalities, bone marrow transplantation on outpatients basis, regimen for elderly, or on hematologic disease in general.

2.3 Data Source and Search Strategy

Two authors (O.E, D.A) conducted independent searches for studies published before 18 Sept 2015 by using Medline (through the PubMed search engine) (http://www.ncbi.nlm.nih.gov/pubmed), the Cochrane Database for Systematic Reviews, the Cochrane Central Register of Controlled Trials (http://community.cochrane.org/editorial-and-publishing-policy-resource/cochrane-central-register-controlled-trials-central,), the Embase

(https://www.embase.com/), and the CINAHL databases (https://www.ebscohost.com/nursing). The key words used in each database are outlined in Appendices 1-3. No language restrictions were applied on the search and all searches were updated until September 2015. Other evaluated resources included: papers presented in meetings and conferences; GreyNet International (http://www.greynet.org/opengreyrepository.html, clinical trials.gov and reference lists of included articles. Identified articles were screened by titles and abstracts through applying the outlined eligibility criteria. For articles with any likelihood of eligibility, exclusions were made after reviewing the full text. For studies published as abstracts, the corresponding authors were contacted by email to seek the full text. Disagreement between researchers about eligibility was resolved by discussion and consensus. Possible duplication was addressed at the stage of full text review and when overlap of reporting from the same dataset was found, the most complete report was included.

Fig. 1 illustrates the search results and it shows that out of a total of 3055 abstracts, only 35 fit the inclusion criteria. The full text of 6 abstracts could not be found even after contacting the corresponding authors. Fourteen studies were excluded because of being a duplicate of the same study in a different year, being a case report, or commentary, or involve BMT. Twenty one studies remained eligible for the review.

Only one non-randomized controlled trial fit the eligibility criteria; all other studies had prospective or retrospective cohort designs. The studies included patients with a variety of leukemia types as shown in Table 1.

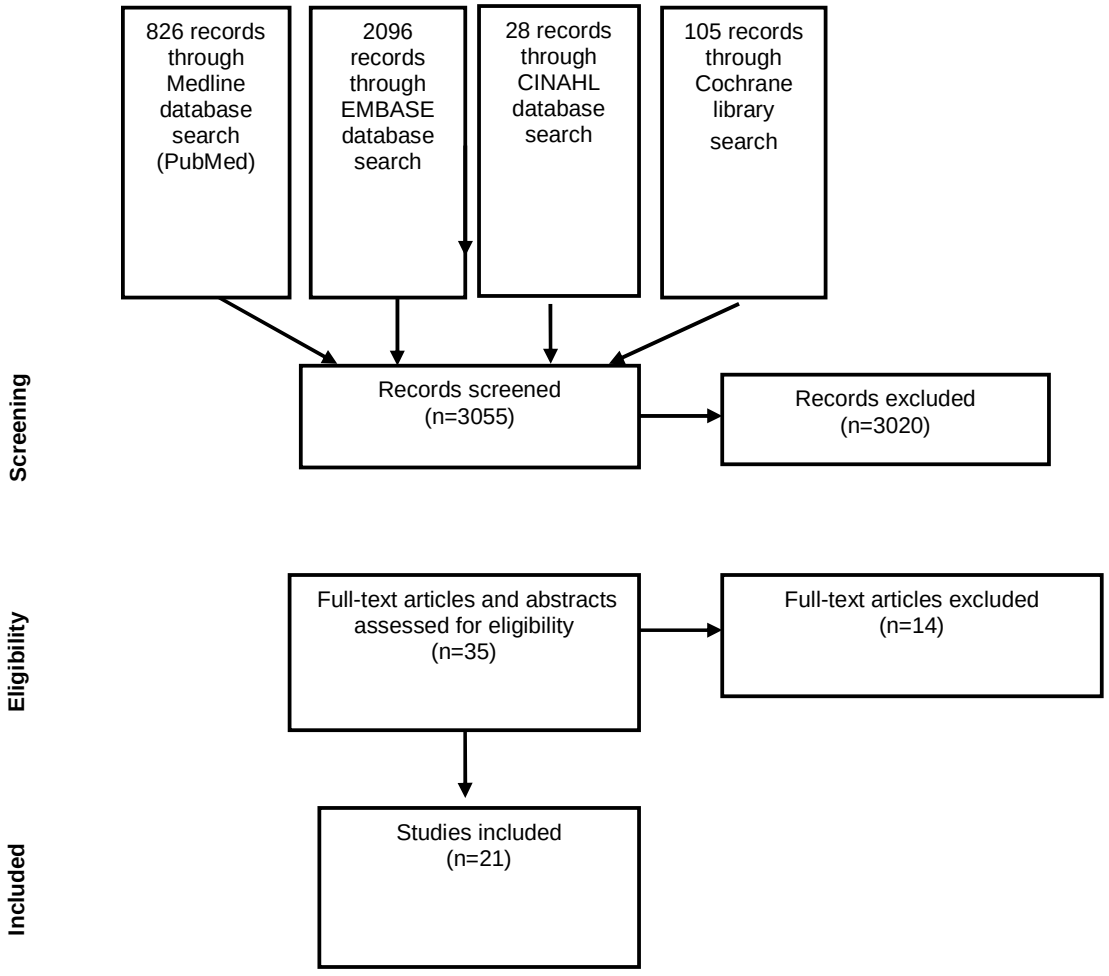


Fig. 1. Search results

2.4 Data Extraction

A detailed data collection form was designed to capture information about each article's population, design and outcome measurements, as well as details of the actual results. It was intended to apply risk of bias tools only to articles conducting comparisons between early discharge versus regular practice.

2.5 Statistical Analysis

Data about studies were entered and tabulated on RevMan version 5.0 which was used to generate forest plots. Meta-analysis was attempted for the following outcomes reported by at least two studies: death; febrile neutropenia and septicemia. Odds ratios (OR) were used for presenting all selected outcomes. Fixed, as well as random effects models, were used for each outcome. Heterogeneity was examined visually. To test for statistical heterogeneity, the I^2 test was used with a significant heterogeneity set at $\geq$ 25% and the Chi-square test was used with an alpha of 0.1.

2.6 Characteristics of Included Studies

The studies included a total of 1850 patients. A weighted mean of the age of all patients could not be obtained because only two studies reported the average age in terms of the mean while seven reported the median and the rest did not report an average age for their patients (Table 1).

Table 2 explains the different types of leukemia in the included studies and it shows that studies were not consistent with regards to the type of leukemia included.

Nine studies, including 1384 patients, attempted early discharge after induction chemotherapy with a total of 976 induction cycles, of which 552 were followed by early discharge of patients according to each study's definition of early discharge. Sixteen studies commented on consolidation therapy with a total of 2130 consolidation cycles in all studies. The majority of consolidation cycles (1745 cycles) were given on outpatient basis or were followed by early discharge, as per each study's definition of early discharge (Tables 3 and 4).

Table 5 summarizes chemotherapy protocols. For induction chemotherapy, most of the studies used (7 + 3) or similar or high dose cytarabine-containing regimens [7,10,19,21,22,24]. The study by Girmenia et al. used the AIDA protocol [all-trans-retinoic acid (ATRA)+ anthracycline idarubicin (IDA)*]* for induction. For consolidation chemotherapy most of the studies used high dose cytarabine.

Studies varied in their definition of outpatient treatment and early discharge; the definition also varied according to whether the patients were at induction or consolidation. In the study by Girmenia et al. [6], which attempted only outpatient consolidation, outpatient therapy included only those patients in their third consolidation cycle while inpatients where those treated inside the hospital for their whole consolidation and were not discharged early. Outpatients in Girmenia et al. [6] study were discharged early at the end of the third consolidation cycle regardless of their blood picture, provided they were in good clinical condition; were not receiving intravenous therapy and were without fever and/or bleeding. In the study by Gillis et al. [10] patients were discharged at the end of chemotherapy administration, regardless of what their white blood cell (WBC) count or platelet counts were and whether they were on induction or consolidation. Naithani et al. [19], Girmenia et al. [17], and Sopko et al. [21] discharged consolidation patients and Ruiz- Argüelles et al. [4] and Walter et al. [25] discharged induction patients after completion of chemotherapy and did not specify any time frame or conditions related to blood count or general condition.

Some studies differentiated between outpatient treatment and early discharge. In the study by Saini et al. [20] outpatients received their entire consolidation chemotherapy on an ambulatory basis while early discharge patients received their chemotherapy as inpatients and were discharged immediately after chemotherapy completion to be followed on an ambulatory basis through their neutropenic phase. During their analysis, Saini et al. [20] classified each consolidation cycle as an outpatient or an early discharge cycle regardless of how the same patient was followed up during the rest of his cycles. A more or less similar classification for ambulatory treatment was introduced in the study by Halim et al. [7] where outpatient treatment was defined as ambulatory administration of chemotherapy and supportive care while early discharge was designated when chemotherapy was given inside the hospital with the patient leaving the hospital before day+15 after chemotherapy or before Absolute Neutrophil Count (ANC) reached 0.5 $x10^9$/L. Inpatients were

those who left the hospital after day+15 after chemotherapy, or after ANC reached 0.5 $x10^9$/L. In Halim's study [7] those definitions applied both to induction and consolidation patients. Allan et al. [5] also used one definition for early discharge for both induction and consolidation cycles. They defined early discharge as that taking place less than ten days after completion of chemotherapy while inpatient treatment in their study referred to remaining inside the hospital for more than ten days after chemotherapy completion. This was not the case however in the study by Savoie et al. [8] who had different definitions for early discharge in induction as compared to consolidation cycles. Early discharge during induction was defined as any discharge after chemotherapy prior to ANC recovery > 0.5 $x10^9$/L while in case of consolidation attempts were made to treat the patients entirely on ambulatory basis. Out of their 73 cycles, 67 were regarded as outpatient cycles. In the study by Eiselea et al. [9] on consolidation chemotherapy, the criteria for early discharge were actually modified along the way. They had started off permitting discharge right after chemotherapy completion and re-admission with the onset of neutropenia, then re-admission was subsequently required only if neutorpenia was accompanied by the occurrence of complications.

Table 6 summarizes the criteria used by studies to judge eligibility of leukemia patients for outpatient treatment or early discharge. The definition of good general condition varied, being defined by Gillis et al. [10] as being fully ambulatory and by Naithani et al. [19] as having no obvious source of infection, being afebrile and not receiving antibiotics.

Care of ambulatory patient was very similar between studies and some institutions offered a near accommodation for out-of-town patients [7]. Yet, studies varied in their definition of near accommodation. According to Halim et al. [7] and Naithani et al. [19] it had to be <1 hour from their day care, but had to be 2 hours by car from hospital according to Girmenia et al. [6]. An ambulatory clinic was made available in all studies. Clinic visits ranged from daily to weekly. Blood and platelet transfusion support was given in day care facilities in asymptomatic patients with hematocrit less than 26% and platelet count less than $10x10^9$/L [25]. Granulocyte colony stimulating factor (G-CSF) was added with the onset of fever [21] or from day 16–18 until neutrophil recovery [20]. A 24 hour telephone line was also provided for patients in some studies [6,22]. Febrile neutropenic patients were mostly reevaluated daily to determine their eligibility for continued ambulatory treatment and in some studies patients were admitted with the onset of fever.

Antimicrobial prophylaxis was likewise managed differently among studies. Table 7 summarizes the antimicrobial prophylaxis given and it shows predominance for the use of fluoroquinolones.

2.7 Outcomes Reported

Reports on the pattern of outcomes differed among studies. The main outcomes reported in all studies were: febrile neutropenia; readmission rate; septicemia; ICU admission and death.

Causes of admission/readmission were mainly fever, sepsis and severe anemia. While some authors reported admitting patients with fever [6,19,21], others admitted patients only for persistent fever [7,8,20,24] whilst some febrile neutropenic patients could continue outpatient treatment [7,6,20,22]. Other criteria of readmission were: hemodynamic instability; bleeding; requirement of antibiotics more than once daily; neutropenic colitis; and failure to thrive due to inadequate care from the care giver [7] and [8]. Allan et al. [5] reported that patients with side effects, e.g febrile neutropenia, mucositis, dehydration, inadequate nutrition, and bleeding were assessed and admitted as necessary. Criteria of readmission were not explicitly reported in the rest of the studies.

2.7.1 Neutropenic fever

Most studies reported some details about the occurrence of neutropenic fever. Some reported admissions as a result of neutropenic fever but because not all studies admitted patients when fever happened, it was also important to note the number of fever episodes independent of the admissions. The duration of fever was reported only in two studies. Only Moller et al. [24] reported fever in terms of episodes per patient and they were four.

2.7.2 Hospitalization days

Details about the time to admission for outpatients and those with early discharge were mentioned only in five studies [5,6,8,10] and [17]. Although a very important parameter, the total duration of hospitalization days for those treated

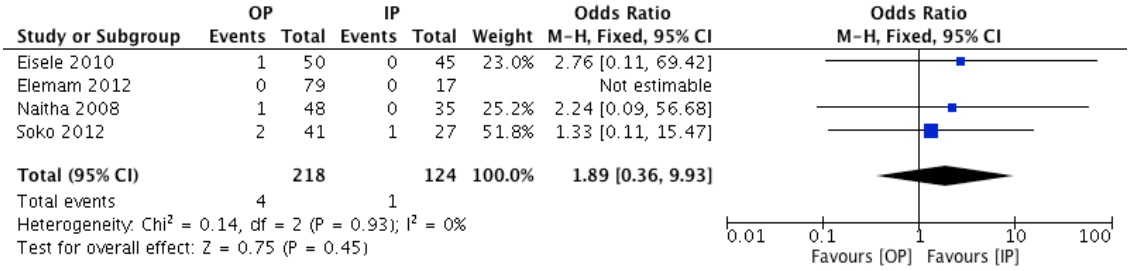
as inpatients and those treated on an outpatient basis was reported only in seven studies. The reporting took different forms: mean ± standard deviation, or median and range. Reduced length of stay as a result of the outpatient treatment strategy was only presented in two studies, which reported that their policy allowed patients to be out of the hospital for 1297 cumulative days (13.2 mean days; range 5–29) representing 76% of the post-consolidation neutropenia period [6,24]. Four studies reported that the cost with early discharge patients were significantly lower than those of inpatient controls [4,9,22] and [25].

3. RESULTS

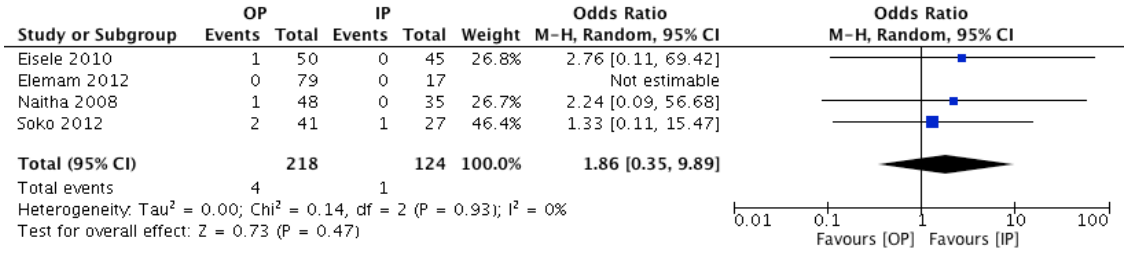
For the 552 induction cycles administered to outpatients, 186 febrile episodes were reported, 53 septicemias and no deaths. Among the 1745 outpatient consolidation cycles, there were 1070 febrile episodes, 129 cases of septicemia and 21 deaths. Out of 2297 cycles of chemotherapy given in the outpatient setting, admission was required in 1088 cycles and 49 of these admissions were to the ICU. Reports on infections during outpatient chemotherapy-induced neutropenia differed mainly by the number of positive cultures or microbial isolates. Two studies reported the occurrence of ciprofloxcin resistant bacteria in patients who received ciprofloxacin prophylaxis [8,14]. Only three studies reported about fungal pneumonia with a total of 23 cases in the outpatient setting. (Tables 3, 4 and 8).

Meta-analysis was attempted for three outcome measures of consolidation therapy namely: death; neutropenic fever episodes; and septicemia. Data was for any other outcome analysis for either consolidation or induction. Since one out of the four studies reported zero deaths, the odds ratio was estimable only in three. The pooled OR of 1.89 numerically favored inpatient treatment, yet this was far from being statistically significant (p=0.45). There was no statistical or visual heterogeneity among studies and the pooled OR differed very slightly between the fixed effects and the random effects models (Fig. 2).

For neutropenic fever episodes, only two studies could be entered in the meta-analysis. The two studies closely embraced the line of no difference from the two sides giving a non-significant pooled OR close to unity. This did not vary between the fixed effects and the random effects models (Fig. 3).



(a)



(b)

Fig. 2. Forest plot for death with outpatient and early discharge consolidation versus death with inpatient consolidation; (a) fixed effect model, (b) random effect model; OP = outpatient; IP = inpatient

Table 1. Characteristics of included studies

Study	Design	Type of leukemia	Start year	End year	Country	No. of patients	Male%	Min age	Max age	Mean age	Median age
Abro, [12] 2013	RC	ALL	1999	2011	NK	44	63.6	17	73		
Allan et al. [5] 2001	RC	AML, APL & BP	Jan 1996	July 1998	Canada	70		18[a]	67[a]		
Allen et al. [13] 2013	RC	AML	2005	2012	USA	50		20	70		
Eiselea et al. [9] 2010	RC	AML	Aug 2003	May 2008	Germany	24	41.7	21	74		59
Elemam et al. [14] 2012	RC	AML, ALL & BP	2005	2010	Saudi Arabia	65	41.5	13	56		
Ferro et al. [15] 2012	PC	AML	2003	2010	USA	347	0	18	85		
Gaya et al. [16] 2014	RC	AML	March 2011	Feb 2014	Spain	29 40[b]	NK	NK	NK	NK	NK
Gillis et al. [10] 1996	PC	AML	Feb 1992	Aug 1993	Israel	22		16	63	NK	40
Girmenia et al. [6] 1999	PC	APL	Jul 1994	Aug 1998		40	37.5	21	72	44	
Girmenia et al. [17] 1999	PC	AML & APL	Jul 1996	Jun 1998		37		NK	NK	NK	NK
Halim et al. [7] 2007	RC	AML	1999	2004	Canada	294	53.1	17	76	46.5	52
Lang et al. [18] 2013	PC	AML	NK	NK	NK	23	NK	20	78	NK	51
Møller et al. [24] 2012	PC	AML, ALL & APL	2004	2007	Denmark	56	53.6	18	74	NK	49[d] 44 [e]
Naithani et al. [19] 2008	RC	AML	NK	NK	India	28	0	6	64		22

Study	Design	Type of leukemia	Start year	End year	Country	No. of patients	Male%	Min age	Max age	Mean age	Median age
Ruiz- Argüelles et al. [4] 1995	PC	AML			Mexico	60	63.3	14	63		
Saini et al. [20] 2011	RC	AML	Oct 2002	Feb 2008	Canada	71	49.3	NK	NK	NK	NK
Savoie et al.[8] 2006	PC	AML& APL	Sep 2001	Oct 2002	Canada	41	41.5	22[a]	67[a]		46[a]
								22[c]	74[c]		51[c]
Sopko et al. [21] 2012	PC	AML			Slovakia	256	55.5	20	66	46.5	
Vaughn et al. [22] 2015	CT[f]	AML	2011	2014	USA	178	49.4	19	73		52
Walter et al. [25] 2011	PC	AML	2009	2010	USA	20	50	19	60		
Ward et al. [23] 2009	RC	AML	2002	2005	Canada	55	69.1	60	84		

a: with induction; b: historical group; c: with consolidation; d: in men; e: in women; f: Non randomized phase 2; *AML = Acute myeloid leukemia; APL = Acute promyelocytic leukemia ; ALL = Acute lymphocytic leukemia; BP = biophenotypic; Min = minimum; Max = maximum; NK: Not known; PC = Prospective cohort; RC = retrospective cohort*

Table 2. Types of included leukemia

Study	Design	AML	Acute lymphocytic leukemia	Acute promyelocytic leukemia	De novo acute leukemia	Secondary leukemia	Treatment-related leukemia	Relapsed leukemia	Biphenotypic
Abro, [12] 2013	Retrospective cohort		X		X				
Allan et al. [5] 2001	Retrospective cohort	X		X	X				X
Allen et al. [13] 2013	Retrospective cohort	X			X				
Eiselea et al. [9] 2010	Retrospective cohort	X			X	X			
Elemam et al. [14] 2012	Retrospective cohort	X	X		X				X
Ferro et al. [15] 2012	Prospective cohort	X			X				
Gaya et al. [16] 2014	Retrospective and prospective cohort	X			X				
Gillis et al. [10] 1996	Prospective cohort	X			X	X		X	
Girmenia et al. [6] 1999	Prospective cohort	X		X					
Girmenia et al. [17] 1999	Prospective cohort	X		X	X				
Halim et al. [7] 2007	Retrospective cohort	X			X	X	X		
Lang et al. [18] 2013	Prospective cohort	X			X				
Møller et al. [24] 2012	Prospective cohort		X	X		X			
Naithani et al. [19] 2008	Retrospective cohort	X			X				
Ruiz- Argüelles et al. [4] 1995	Prospective cohort	X			X				
Saini et al. [20] 2011	Retrospective cohort	X			X				
Savoie et al. [8] 2006	Prospective cohort	X		X	X			X	
Sopko et al. [21] 2012	Prospective cohort	X			X				
Vaughn et al. [22] 2015	Non randomized phase 2	X			X			X	
Walter et al. [25] 2011	Prospective cohort	X			X			X	
Ward et al. [23] 2009	Retrospective cohort	X			X				

Table 3. The outcome of inpatients and outpatients induction cycles

Author	Total induction cycles (N)	IP induction (N)	OP Induction (N)	IP induction episodes (N)	OP induction episodes (N)	IP induction deaths (N)	OP induction deaths (N)	IP induction septicemia (N)	OP induction septicemia (N)
Allan et al. [5] 2001	19	9	10	9	9	1	0	NK	NK
Ferro et al. [15] 2012	317	58	259	NK	NK	NK	NK	NK	NK
Gillis et al. [10] 1996	33	29	4	NK	NA	NA	NK	NK	NK
Halim et al. [7] 2007	328	NK	34	NK	NK	NK	NK	50	5
Møller et al. [24] 2012	73	NA	73	NA	25	NA	0	NA	6 pt
Vaughn et al. [22] 2015	136	29	107	NK	108	0	4	4	37
Ruiz- Argüelles et al. [4] 1995	24	NA	24	NA	7	NA	0	NA	4
Savoie et al. [8] 2006	26	NA	26	NA	21 (14 pts)*	NA	0	NA	1
Walter et al. [25] 2011	20	5	15	NK	16	0	0	NK	NK

N = number; Episode = febrile episode; NK = Not known; NA = Not applicable; IP = inpatient; OP = outpatient
**21 febrile episodes occurred in 14 patients*

Table 4. The outcome of inpatients and outpatients consolidation

Author	Total consolidation (N)	IP consolidation (N)	OP consolidation (N)	IP consolidation deaths (N)	OP consolidation deaths (N)	IP consolidation episodes (N)	OP consolidation episodes (N)	IP consolidation septicemia (N)	OP consolidation septicemia (N)
Abro, [12] 2013	270	78	148	NK	NK	45	184	NK	NK
Allan et al. [5] 2001	30	NA	30	NA	3	NA	25	NK	NK
Allen et al. [13] 2013	NK	NK	71	NK	NK	NK	NK	NK	NK
Eiselea et al. [9] 2010	95	45	50	0	1	NK	18	6	8
Elemam et al. [14] 2012	96	17	79	0	0	11	23 with prophylaxis+ 33 without	NK	NK
Gaya et al. [16] 2014	116	NA	116	NA	0	NA	17 with AHP+45 without AHP	NA	NK
Gillis et al. [10] 1996	53	NK	46	NK	NK	NK	NK	NK	NK
Girmenia et al. [6] 1999	104	NA	98	NA	1	NA	40	NA	16
Girmenia et al. [17] 1999	127	NA	127	NA	1	NA	68	NA	34
Halim et al. [7] 2007	295	132	163	NK	NK	NK	NK	44	27
Lang et al. [18] 2013	61	NA	61	NA	0	NA	2	NA	NK
Møller et al. [24] 2012	129	NA	129	NA	0	NA	40	NA	8 pt
Naithani et al. [19] 2008	83	35	48	2	1	24	25	7	1
Saini et al. [20] 2011	473	71	402	NK	9	NK	399	NK	

Author	Total consolidation (N)	IP consolidation (N)	OP consolidation (N)	IP consolidation deaths (N)	OP consolidation deaths (N)	IP consolidation episodes (N)	OP consolidation episodes (N)	IP consolidation septicemia (N)	OP consolidation septicemia (N)
Savoie et al.[8] 2006	73	NA	67	NA	0	NA	54 (39 cycles)	NA	13
Sopko et al. [21] 2012	56	15pt	41	1	2	12	23	7	22
Ward et al. [23] 2009	70	NK	70	NK	0	NK	70	NK	NK

Table 5. Chemotherapy regimens

Name of 1st author & publication year	Type of leukemia	Induction	Consolidation	Chemotherapy
Abro, [12] 2013	ALL	No	Yes	Hyper-CVAD
Allan et al. [5] 2001	AML, APL & Biphenotypic	Yes	Yes	Mitoxantrone 12 mg/m^2 for 3 days and cytosine arabinoside 1g bid for 5 days Daunorubicin 60 mg/ m^2 for 3 days and cytosine arabinoside 100 mg/ $m^2$for 7 days by continous infusion Consolidation consisted of 2 cycles of Mitoxantrone 6mg/m^2 for 3 days and cytosine arabinoside 2g/m^2q12 h for 3 days Or 2 cycles of Daunorubicin 45 mg/ m^2 for 3 days and cytosine arabinoside 3g/m^2q12 h days 1,3,and 5 Patients with acute promyelocytic leukemia received all-trans retinoic acid (ATRA) therapy along with induction and consolidation.
Allen et al. [13] 2013	AML	No	Yes	Cytarabine
Eiselea et al. [9] 2010	AML	No	Yes	daunorubicin plus cytarabine in a 3 +7 schedule., 7 + 3 gemtuzumab ozogamicin (GO)
Elemam et al. [14] 2012	AML, ALL & acute biphenotypic	No	Yes	High dose cytarabine
Ferro et al. [15] 2012	AML	Yes	No	7+3 cytarabine with additional agents in few cases High/ intermediate dose cytarabine with additional agents in few cases
Gaya et al. [16] 2014	AML	No	Yes	Consolidation therapy for AML
Gillis et al. [10] 1996	AML	Yes	Yes	Induction chemotherapy consisted of daunorubicin (45mg/ m^2 daily for 3 days; over age 60 reduced to 30 mg/ m^2 daily for 3 days) and cytosine arabinoside (100 mg/ m^2/day by continuous infusion for 7 days). This was followed by consolidation with high dose cytosine arabinoside(1-3 g/ m^2, twice daily for 5-6 days) and an additional cycle consisting of etoposide (100 mg/ m^2, days1-5) and mitoxantrone (12 mg/ m^2, days 1-3). Patients who relapsed were treated either with one of the above protocols or with high dose cytosine arabinoside (3 grams/ m^2 daily for 5 days) and high dose mitoxantrone(20 mg/ m^2, days 1-2).
Girmenia et al. [6] 1999	APL	No	Yes	Treatment schedule of the AIDA protocol Induction ATRA 45 mg/ m^2/day p.o.+ Idarubicin 12 mg/ m^2/day, by brief i.v. infusion days 2, 4, 6, 8 Complete remission: 3 consolidation courses

Name of 1st author & publication year	Type of leukemia	Induction	Consolidation	Chemotherapy
				Course 1:Ara-C 1 g/ m^2/day, by i.v. infusion lasting 6 hours, days 1, 2, 3, 4,Idarubicin 5 mg/m2/day, by brief i.v. infusion, days 1, 2, 3, 4 Course 2:Mitoxantrone 10 mg/ m^2/day, by brief i.v. infusion, days 1, 2, 3, 4, 5, VP-16 100 mg/ m^2/day, by i.v. infusion lasting 45–60 min, days1, 2, 3, 4, 5 Course 3: Idarubicin 12 mg/ m^2, by brief i.v. infusion, day 1,Ara-C 150 mg/ m^2, every 8 h subcutaneously, days 1, 2, 3, 4, 5,6-Thioguanine 70 mg/ m^2, every 8 h p.o., days 1, 2, 3, 4, 5
Girmenia et al. [17] 1999	AML & APL	No	Yes	AML-10 EORTC/GIMEMA AML-13 EORTC/GIMEMA AIDA GIMEMA
Halim et al. [7] 2007	AML	No	Yes	7 + 3 or similar or high-dose cytarabine (HIDAC).containing regimens
Lang et al. [18] 2013	AML	No	Yes	Consolidation therapy for AML
Møller et al. [24] 2012	AML, ALL & APL	Yes	Yes	Induction → consolidation AMLDA 3 + 10 → DA 8 + 3 DA 3 + 10 w. GO → ADE 8 + 3 + 5 ADE 10 + 3 + 5 → MACE ADE 10 + 3 + 5 w. GO → MACE+GO FLAG-Ida → HD-Ara-C FLAG-Ida w. GO → HD-Ara-C+GO 3 + 7 Ida-Ara-C → MIDAC 2 + 5 Ida-Ara-C → FLAG-Ida FLAG-Mitox → 2 + 5/3 + 7 Ida-Ara-C Ida+ATRA → FLAG-Mitox MACE w..GO → FLAG HD-Ara-C w. GO → Ida Mitox GO ALL CTX-Dau-Vin-pred-Asp → Hyper-CVAD Hyper-CVAD → HD-MTX+HD-Ara-C HD-Ara-C – Mitox → HD-Ara-C – Mitox HD-Ara-C – HD-MTX → HD-CTX HD-MTX.
Naithani et al. [19] 2008	AML	No	Yes	Standard 3+7 chemotherapy, after complete remission (CR) consolidation chemotherapy with 3 cycles of high dose cytarabine was given
Ruiz- Argüelles et al. [4] 1995	AML	Yes	No	Ara-C 100 mg/m^2 continuous infusion d1-7 and adriamycin 45mg/m^2/d bolus d1-3 Mitoxantrone 10 mg/ m^2/day, IV for 5 days VP-16 100 mg/ m^2/day, by IV for 5 days.
Saini et al. [20] 2011	AML	No	Yes	Standard induction chemotherapy daunorubicin plus cytarabine in a 3 +7 schedule. Under age 60, each cycle consisted of cytarabine 3 g/ m^2 IV q12h x 6 doses on Days 1, 3, and 5 (Doses 2, 4, and 6 given at home via an ambulatory infusion pump [AIP]) plus daunorubicin 45 mg/ m^2 IV on Days 1 and 2.

Name of 1st author & publication year	Type of leukemia	Induction	Consolidation	Chemotherapy
				For patients age 60, cycle 1 (C1) consisted of daunorubicin 60 mg/ m^2 IV daily for 3 days plus cytarabine 100 mg/ m^2continuous infusion daily x 7 via AIP. Consolidation #2 (C2) consisted of mitoxantrone 10 mg/ m^2 IV plus etoposide 100 mg/ m^2 IV once daily on Days 1-5 For patients with a decreased left ventricular ejection fraction, amsacrine 100 mg/ m^2 was substituted for the anthracycline.
Savoie et al. [8] 2006	AML& APL	Yes	Yes	HIDAC/DaunoCytarabine 3.0 gm/ m^2/d days 1–6 and daunorubicin45 mg/ m^2/d days 1–3 7 + 3 Cytarabine 200 mg/ m^2/d days 1–7 and daunorubicin 45 mg/ m^2/d days 1–3 AML-M3 Cytarabine 200 mg/m2/d days 1–7, daunorubicin 60 mg/ m^2/d days 1–3 and ATRA 30 mg/ m^2/d days 1–60 VP-16/CY Etoposide 2.4 gm/ m^2 day 1 and cyclophosphamide 50 mg/kg/d on days 3–5 Carbo/ara C Cytarabine 1.5 gm/m2/d bid days 1–4 and carboplatin300 mg/ m^2/d CIVI days 5–8 5 + 2 Cytarabine 200 mg/ m^2/d days 1–5 and daunorubicin30 mg/ m^2/d days 1–2
Sopko et al. [21] 2012	AML	No	Yes	Anthracyclines and cytarabine followed by either high dose cytarabine consolidation or BMT
Vaughn et al. [22] 2015	AML	Yes	No	Standard intensity regimens 7+3 or 7+3 like therapy and high intensity regimens containing cytarabine doses of more than 1g/m^2
Walter et al. [25] 2011	AML	Yes	No	7 + 3 ±GO(gemtuzumab ozogamicin),Idarubicin/HiDAC/pravastatin G-CLAC, FLAM, MEC/ gemtuzumab ozogamicin/cyclosporine FLAG/ gemtuzumab ozogamicin
Ward et al. [23] 2009	AML	No	Yes	Daunorubicin 60 mg/ m^2 for 3 days and cytosine arabinoside 100 mg/ $m^2$for 7 days by continous infusion

Hyper CVAD: Cyclophosphamide 200 mg/m2 BID days 1–3, vincristine 2 mg days 1 and 8, doxorubicin 50 mg/m2 day 4, dexamethasone 40 mg days 1–4 and 11–14, methotrexate 12 mg intrathecallyday 1, cytarabine 100 mg intrathecally day 8. AIDA= all-trans-retinoic acid (ATRA)+ anthracycline idarubicin (IDA)
ADE: Cytarabine 100 mg/m2 bid days 1–10 (days 1–8 in consolidation),daunorubincin 50 mg/m2 days 1, 3 and 5, etoposide 100 mg/m2 days 1–5.
DA: As above without etoposide.
GO: 3 mg/m2 day 1.
FLAG: Fludarabine 30 mg/m2 days 1–5, cytarabine 2 g/m2 days 1–5, lenograstim 263 microg. sc days 0–6.
FLAG-Ida: FLAG with idarubicin 8 mg/m2 days 3–5.
3 + 7/2 + 5 Ida-Ara-C: Idarubicin 12 mg/m2 days 1–3, cytarabine 200 mg/m2 daily by continuous infusion days 1–7/days 1–5.
FLAG-Mitoxantrone: FLAG with mitoxantrone 10 mg/m2 days 1–3.
MACE: Amekrin 100 mg/m2, cytarabine 200 mg/m2 daily, etoposide 100 mg/m2 all days 1–5.
HD-Ara-C: Cytarabine 1.5 mg/m2 BID days 1, 3 and 5, or 3 mg/m2 BID days 1, 3 and 5.
MIDAC: Cytarabine 1 g/m2 BID days 1–3, mitoxantrone 10 mg/m2 days 1–5.
Ida+ATRA: Idarubicine 12 mg/m2 days 1, 3, 5, 7, all trans retinoic acid 22.5 mg/m2 BID.
CTX-Dau-Vin-Pred-Asp: Cyclophosphamide 1.2 g/m2 day 1, daunorubicine 45 mg/m2 days 1–3, vincristine 2 mg days 1, 8, 15, 22, asparaginase 6.000 U/m2 days 5, 8, 12, 15, 19, 22.
Hyper CVAD: Cyclophosphamide 200 mg/m2 BID days 1–3, vincristine 2 mg days 1 and 8, doxorubicin 50 mg/m2 day 4, dexamethasone 40 mg days 1–4 and 11–14, methotrexate 12 mg intrathecallyday 1, cytarabine 100 mg intrathecally day 8.
HD-Ara-C – Mitox: Cytarabine 2 g/m2 BID days 1–4, mitoxantrone 12 mg/m2 days 5 and 6, lenograstim 263 microg. sc daily from day 7.
HD-MTX – HD-Ara-C: MTX 1 g/m2 continuous infusion over 24 h (isovorin rescue), cytarabine 3 g/m2 BID days 2–3., solu-medrol 50 mg iv BID days 1–3, methotrexate 12 mg intrathecally day 1,cytarabine 100 mg intrathecally day 8.
Ida: Idarubicine 7 mg/m2 days 1–4.
Mitox: Mitoxantrone 10 mg/m2 days 1–5.
HD-CTX: Cyclophosphamide 2 g/m2.
HD-MTX: Methotrexate 3 g/m2 with isovorin rescue.
$"3+7" ± gemtuzumab ozogamicin (GO):daunorubicin (45-90 mg/m2) x 3 days + cytarabine 100 mg/m2x7 days GO (6 mg/m2) x 1 day;idarubicin (12 mg/m2) x 3 days/HiDAC (cytarabine 1,500 mg/m2) x 4 days/pravastatin;
G-CLAC: G-CSF/clofarabine (25 mg/m2) x 5 days/HiDAC (cytarabine 2,000 mg/m2) x 5 days;
FLAM: flavopiridol (50 mg/m2) x 3 days/HiDAC (cytarabine 2,000 mg/m2/72 h) x 1/mitoxantrone (40mg/m2) x 1 day;
MEC/GO/cyclosporine: mitoxantrone (6 mg/m2) x 5 days/etoposide (80mg/m2) x 5 days/cytarabine (500 mg/m2) x 5 days/GO (3 mg/m2) x 1day/cyclosporine;
FLAG/GO: fludarabine (30 mg/m2) x 5 days/HiDAC (cytarabine 2,000 mg/m2) x 5 days/GO (3 mg/m2) x 1 day

Table 6. Inclusion criteria for outpatient / early discharge in included studies

Name of first author and publication year	Criteria for OP/early discharge
Abro, [12] 2013	Whenever possible
Allan et al. [5] 2001	Absence of fever and medical complication ,patients required a principal care giver or family member availabe in case of distress .patients had to live or stay within 50-km radius from the hospital
Allen et al. [13] 2013	Insurance coverage for outpatients cytarabine and availability of local housing/ caregiver
Eiselea et al. [9] 2010	Absence of fever (T < 38 ℃), hemodynamic stability, introduction of an appropriate prophylactic antimicrobial regimen, residence within 60 min of our center, a willing and able local caregiver, and absence of serious co-morbidities.
Elemam et al. [14] 2012	Those requiring inpatient care during chemotherapy administration (e.g. ICU care, care for severe fungal infections, or resistant severe thrombocytopenia) were excluded.
Ferro et al. [15] 2012	Not mentioned
Gaya et al. [16] 2014	All consecutive patients with AML without significant co-morbidities or active febrile complications who received consolidation chemotherapy and lived within 60 minutes of the hospital were included in the at-home program (AHP)
Gillis et al. [10] 1996	Good general condition (i.e., fully ambulatory) had no obvious source of infection, were afebrile and were not receiving antibiotics
Girmenia et al. [6] 1999	Limited distance between patient residence and hospital location (2 hours, by car). Patients living too far from the hospital were allocated to a nearby patient residence.
Girmenia et al. [17] 1999	Good clinical condition, without fever and/or bleeding and not receiving intravenous therapy. Major complications occurring during the previous induction therapy were not considered a contraindication to early discharge after consolidation, relatively short distance between the patient's residence and the hospital (< 2 hours, by car). Patients living far from the hospital were allocated in a nearby residence for patients.
Halim et al. [7] 2007	Clinically stable, had accommodations <1 hour from our day care and, had a willing and able caregiver
Lang et al. [18] 2013	All patients deemed sufficiently fit to undergo consolidation chemotherapy as outpatients or to be monitored on an ambulatory basis following inpatient chemotherapy.
Møller et al. [24] 2012	Patients had to live within a 120-kilometer distance from the hospital, deemed mentally capable to comply with given instructions and with a spouse or relative present during night hours. Patients with severe infections and/or being refractory to platelet transfusions could not be treated in an outpatient setting
Naithani et al. [19] 2008	(a) no fever or infection; (b) location of residence nearby; (c) ability to come to hospital within one hour if fever developed or condition deteriorated. They had telephone access to the study team.
Ruiz- Argüelles et al. [4] 1995	No fever nor obvious infections were present and their Karnofsky score was 100%.
Saini et al. [20] 2011	Acceptable Eastern Cooperative Oncology Group (ECOG) performance status (PS), were able to understand instructions and had an available caregiver at home, exclusion criteria included anticoagulation monitoring ,co morbidities or poor PS , continuing admission from induction ,difficult induction, ongoing fungal infection ,or other reasons , difficult first consolidation and patient preference.
Savoie et al. [8] 2006	Absence of fever (T < 38.3˚C), introduction of an appropriate prophylactic or therapeutic antimicrobial regimen, hemodynamic stability, and resolution of any coagulopathy, availability of an accommodation within 60 min of the centre, a willing and able caregiver and the absence of serious co-morbidities.
Sopko et al. [21] 2012	No signs of infection or bleeding, good physical condition, no intravenous therapy, Patient choice and Possibility to arrive early to the clinic.

Name of first author and publication year	Criteria for OP/early discharge
Vaughn et al. [22] 2015	Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, bilirubin level less than or equal to 3 times the upper limit of normal, glomerular filtration rate at least 25% of the lower limit of normal, and no clinical signs of heart failure or uncontrolled bleeding. Need for intravenous (IV) antimicrobial agents did not preclude early hospital discharge, Residency within 60 minutes of the study center and a reliable caregiver, and willingness to frequently follow up at the primary outpatient care facility.
Walter et al. [25] 2011	ECOG performance status of 0-1, bilirubin 2.5 times or below upper limit of normal (ULN), SGOT and SGPT 1.5xULN or below, serum creatinine 1.5xULN or below, left ventricular ejection fraction 40% or over, no intravenous antimicrobial therapy, no active bleeding, and no refractoriness to platelet transfusions, agreeable to close outpatient follow up, and having a reliable caregiver and residency within 30 minutes of the Study Center.
Ward et al.[23] 2009	According to the physician discretion

AHP: At-home program , SGOT: Serum glutamic oxaloacetic transaminase, SGPT: serum glutamic-pyruvic transaminase ULN: upper limit of normal
ECOG: Eastern Cooperative Oncology Group (ECOG)

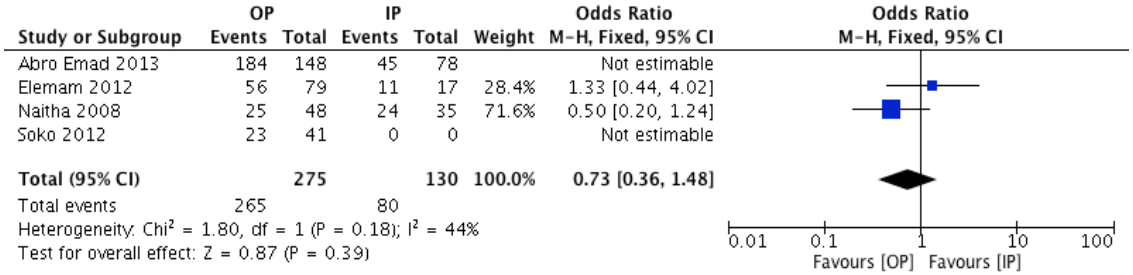
Table 7. Description of chemoprophylaxis

Name of 1st author & publication year	Chemoprophylaxis
Abro, [12] 2013	Not mentioned
Allan et al. [5] 2001	Patients did not receive prophylactic oral antibiotics.
Allen et al. [13] 2013	Not mentioned
Eiselea et al. [9] 2010	Cotrimoxazole, in combination with colistin and oral amphotericin B.
Elemam et al. [14] 2012	Ciprofloxacin 500mg PO BID, Fluconazole 400mg PO daily; and Acyclovir 200mg PO TID until neutrophil count had recovered to >1.0 × 10^9/L, and G-CSF 300 mcg SC daily once their ANC had fallen to 0.5 × 10^9/L and was continued till ANC is>1.0 × 10^9/L
Ferro et al. [15] 2012	Not mentioned
Gaya et al. [16] 2014	Oral levofloxacin (500 mg daily), oral posaconazole (200 mg, three times per day) and intravenous ceftriaxone during the neutropenic (<0.5 x109/L) period
Gillis et al. [10] 1996	Prophylactic oral antibiotics were not prescribed.
Girmenia et al. [6] 1999	Oral ciprofloxacin (500 mg twice a day) and anti-hemorragic prophylaxis with oral tranexamic acid (100 mg/kg/day) and prednisone (25 mg/day) until increase of PMN to1× 10^9/L and of PLTS to 50 × 10^9/L respectively.
Girmenia et al. [17] 1999	Oral ciprofloxacin (500 mg BID) and with oral tranexamic acid (100 mg/kg/day) plus prednisone (25 mg/day), which were administered until neutrophils rose to 1× 10^9/L and platelets to 50× 10^9/L , respectively
Halim et al. [7] 2007	Ofacyclovir 600 mg PO. QID or valacyclovir 500 mg PO daily. (If herpes simplex virus positive), and fluconazole 200–400 mg PO. Daily Or itraconazole 200 mg PO. BID (if previously proven or probable Aspergillus infection) until ANC recovery. Inpatients did not receive prophylactic antibacterial prophylaxis. After 1 September 2001, ciprofloxacin 500 mg PO BID was added as antibacterial prophylaxis to ambulatory patient, starting on the day following chemotherapy or on the day of discharge until ANC recovery.
Lang et al. [18] 2013	Levofloxacin and posaconazole as per local protocol

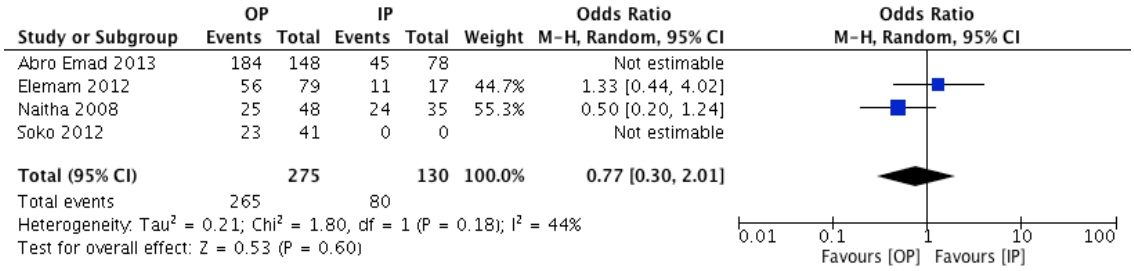
Name of 1st author & publication year	Chemoprophylaxis
Møller et al. [24] 2012	Ciprofloxacine 500 mg PO BID(twice daily), amoxicillin／clavulanic acid 500／125 mg TID (three times daily) and fluconazole 400 mg QD (once daily). Patients with a history of herpes were given acyclovir 400 mg TID. In case of allergy to penicillins, clindamycin 600 mg TID was given. Antibiotic prophylaxis was continued until neutrophils rose above 0.5×10^9/L.
Naithani et al. [19] 2008	Prophylactic ciprofloxacin 500 mg twice daily and fluconazole 200 mg/day
Ruiz- Argüelles et al. [4] 1995	Ciprofloxacin250 mg BID,cotimoxazole (trimetoprim 160 mg ,sulfamethoxazole 800 mg PO BID and itraconazole 100 mg/day po until ANC is>1.0×10^9/L
Saini et al. [20] 2011	Ciprofloxacin 500 mg PO q12 hours, amoxicillin 500 mg PO q8 hours and fluconazole 400 mg PO daily, starting on Day 8 of the chemotherapy cycle and continuing until absolute neutrophil count (ANC) > 0.5×10^9/L. All chemotherapy, transfusions and IV antibiotics were administered via central venous catheters (CVC), usually double lumen Hickman lines placed prior to the start of induction chemotherapy.
Savoie et al. [8] 2006	From the day following the last dose of chemotherapy, all patients received antimicrobial prophylaxis with Ciprofloxacin 500 mg PO BID. Acyclovir 600 mg PO QID or Valacyclovir 500 mg PO daily was used if the HSV IgG titre was positive; Fluconazole 200 to 400 mg PO daily was used as antifungal prophylaxis or, in cases of previously documented or probable invasive fungal infection, Itraconazole 200 mg PO BID. The prophylactic antimicrobials were continued till the ANC reached 0.5×10^9/L
Sopko et al. [21] 2012	Not mentioned
Vaughn et al. [22] 2015	All patients were prescribed prophylactic antimicrobial agents(levofloxacin, fluconazole, and acyclovir or medications with similar antimicrobial coverage)until peripheral blood cell count recovery
Walter et al. [25] 2011	Levofloxacin, fluconazole, and acyclovir (or similar medications) and continued until ANC was 0.5
Ward et al. [23] 2009	Oral antibiotics and antifungal prophylaxis was used.

BID (twice daily TID (three times daily) QD (once daily) absolute neutrophil count (ANC) central venous catheters (CVC) QID (four times daily) PO (per oral)

The case was different with septicemia, with three estimable ORs. The fixed effects model gave a pooled OR of 0.43 in favor of outpatient (OP) consolidation with a 95%CI of 0.27-0.69. There was significant heterogeneity however by both the I^2 and the Chi square that gave 64% and a p value of 0.06 respectively. Using the random effects model resulted in very little change in the OR with a much wider 95% CI that spanned the line of no difference (0.15-1.34) (Fig. 4).

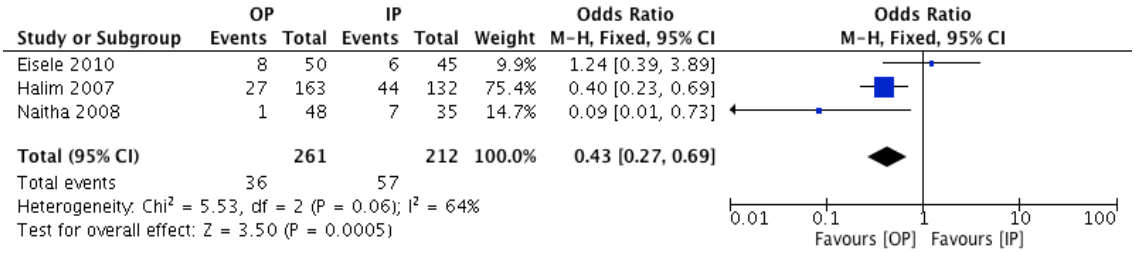


(a)

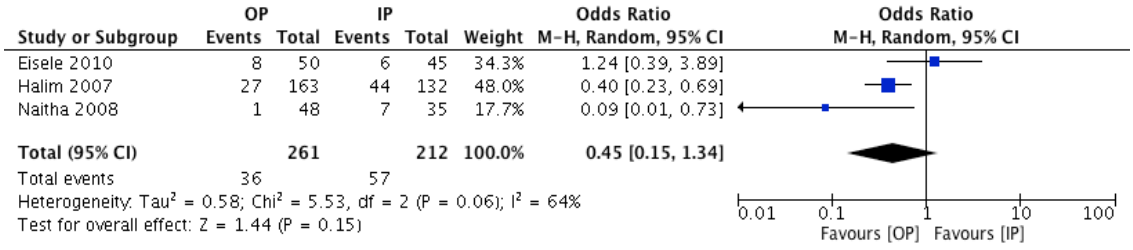


(b)

Fig. 3. Forest plot for neutropenic fever episodes with outpatient and early discharge consolidation versus inpatient consolidation therapy; (a) fixed effect model, (b) random effect model



(a)



(b)

Fig. 4. Forest plots for septicemia episodes with outpatient and early discharge consolidation versus inpatient consolidation therapy; (a) fixed effect model, (b) random effect model

Table 8. Treatment outcome

Name of 1st author & publication year	Number of OP admissions	OP ICU admissions	OP Fungal pneumonia/ infection
Allan et al. [5] 2001	25	1	NK
Allen et al. [13] 2013	20	NK	NK
Eiselea et al. [9] 2010	48	0	0
Elemam et al. [14] 2012	23 with prophylaxis+35 without	0	NK
Ferro et al. [15] 2012	158	NK	NK
Gaya et al. [16] 2014	45 without AHP+ 3 with AHP	NK	NK
Gillis et al. [10] 1996	47	2	0
Girmenia et al. [6] 1999	41	3	0
Girmenia et al. [17] 1999	54	5	1
Halim et al. [7] 2007	27	1	3
Lang et al. [18] 2013	21	2	NK
Møller et al. [24] 2012	76	1	9
Naithani et al. [19] 2008	25	0	0
Ruiz- Argüelles et al. [4] 1995	7	0	0
Saini et al. [20] 2011	296	21	
Savoie et al. [8] 2006	23 (9 pts + 14 cycles)	3	6
Sopko et al. [21] 2012	24	1	0
Vaughn et al. [22] 2015	93	9	4
Walter et al. [25] 2011	19	0	0
Ward et al. [23] 2009	36	NK	NK

OP = outpatient, NK= Not known

It was not possible to compare the outcome based on the antimicrobial prophylaxis given the small number of comparative studies and also due to the fact that only one study (that of Allen et al. 2001) did not give prophylaxis.

4. DISCUSSION

In the past, chemotherapy was given only on an inpatients basis [26]. With the improvement of supportive care over time, and the introduction and standardization of prophylactic antimicrobial chemotherapy regimens, some institutions were more willing to discharge their patients early or, in some cases, treat them entirely as outpatients. The anticipated outcomes included: a reduction of hospital acquired infections (HAIs); reduction of healthcare costs; and improvement in the patient's quality of life [4]. However, the practice of outpatients treatment and early discharge of leukemia patients remains highly variable between different institutions, as do the choice of patients for such modality and the precautions taken [27]. The outcomes of outpatient treatment have not been previously formally compared with strict inpatient management. Hence the need for this systematic review which aimed to quantify the effect of early discharge and outpatient treatment of leukemic patients on important outcome parameters.

The studies reporting on outpatient treatment were largely observational ones and mostly consisted of reports about the outcome of patient treatment for acute leukemia after a certain paradigm shift in their institutions towards early discharge. Hence none of those studies showed randomization and only nine were comparative. Even in the case of the latter, comparison could not be directly made between the group of inpatients on one hand and outpatients or early discharge on the other, since the eligibility of patients for each treatment regimen differed.

It was clear that although consolidation therapy is quite intense. Some institutions attempted early discharge after induction. Differences existed between institutions regarding their definition of early discharge and regarding the eligibility of patients for it. Yet, the minimum requirements: were absence of fever; hemodynamic stability; nearby residence to the treatment center; available caregiver; and absence of serious co-morbidities. The criteria became less stringent as more confidence was gained over the years in antimicrobial prophylaxis and the availability of other forms of supportive care such as colony stimulating factors. Other factors that determined differences in inpatient selection for early discharge were the preparedness of each center to promptly and properly manage therapy complications for patients (e.g. daycare facility,

availability of communication and availability of lodging). This can help in the development of guidelines that can list the minimum requirements for early discharge. Such requirements can always be revised based on the continuing advances in cancer treatment modalities.

Although early discharge of leukemia patients largely affects economic, social and clinical aspects, almost none of the studies comprehensively commented on these aspects. Even within each aspect, outcome reporting was very heterogeneous among studies. Other important clinical outcomes such as: cost of care; fungal infection; and quality of life were not uniformly reported in the studies and could not be analyzed. Economic outcome measures were very heterogeneously reported and could not be analyzed. Febrile neutropenic episodes, septicemia and death were the most frequently reported and were the only universal outcomes for which metaanalysis could be attempted. Very few studies could be combined for each, and it could only be done for consolidation and not for induction.

The pooled effect showed no statistical significant results for mortality with early discharge patients during consolidation (95%CI: [0.36; 9.93]), but favored inpatients. Neutropenic febrile episodes favored outpatients (95%CI of [0.36- 1.48]).

Results on septicemia during consolidation were consistently in favor of outpatient/early discharge treatment. Visually, two of the three studies analyzed, fairly agreed in favor of outpatient treatment. Statistical significance was obtained with the fixed effects model (95%CI of [0.27-0.69]), but not with a wider CI with random effects model. There is a trend towards reduced septicemia incidence with outpatient management (95% CI of [0.15-1.34].

The influence of antimicrobial prophylaxis on the outcome could not be commented upon in this review, since none of the studies included this outcome in their designs.

Although this SR could not perfectly combine results of several studies regarding many important outcomes of acute leukemia treatment, it sheds light on the similarities and differences between treatment approaches for such patients. It also highlights the differences in reporting of study results dealing with this important aspect of care of acute leukemia patients. The exact direction and magnitude of impact of early discharge of acute leukemia patients can only be estimable by well-planned randomized controlled trials. Yet, observational studies and reports of individuals' experiences are still a very valuable source of information. However, there should be more uniformity and comprehensiveness in terms of outcome reporting.

5. CONCLUSION

Studies reporting on outpatient and early discharge of acute leukemia are largely observational and highly heterogeneous. A trend towards a reduced incidence of septicemia was observed with early discharge. The effect of other clinical outcome measures was unclear. Reporting on social and economic impact was suboptimal. More observational studies are needed with uniform and comprehensive outcome reporting. Randomized controlled trials are necessary to compare chemotherapy administration in the outpatient versus inpatient setting to determine eligibility criteria for early discharge. It is also necessary to define: which population is best suited for outpatient therapy, calculate the cost effectiveness of this method; and measure patient satisfaction and quality of life.

CONSENT

It is not applicable.

ETHICS APPROVAL

This article does not contain any studies with human participants performed by any of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Appendix 1. PubMed search strategy

PubMed search was done on 15/Sept/2015	
1	Leukemia
2	Leucocythaemia
3	Leukemias
4	"Nonlymphoblastic, Acute"
5	Acute leukemia
6	"Leukemia, Nonlymphocytic, Acute"
7	"Myeloblastic Leukemia, Acute"
8	"Acute Myeloblastic Leukemia"
9	"Myeloblastic Leukemias, Acute"
10	"Myelocytic Leukemia, Acute"
11	"Acute myelocytic leukemia"
12	"Myelogenous Leukemia, Acute"
13	"Nonlymphoblastic Leukemia, Acute"
14	"Acute Nonlymphoblastic Leukemia"
15	"Nonlymphoblastic Leukemias, Acute"
16	"Acute Myelogenous Leukemias"
17	"Myeloid Leukemia, Acute, M1"
18	"Leukemia, Myeloid, Acute, M2"
19	"Acute Myeloid Leukemia without Maturation"
20	"Leukemia, Biphenotypic, Acute"
21	"Leukemia, Myelogenous, BCR-ABL Positive"
22	"Precursor B-Cell Lymphoblastic Leukemia-Lymphoma"
23	“Precursor T-Cell Lymphoblastic Leukemia-Lymphoma”
24	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25	"Outpatient Care"[
26	"Ambulatory Care"
27	“Outpatient Health Service”
28	“Outpatient Health Services”
29	“Services, Outpatient Health”
30	“Clinic Visits”
31	“Clinic Visit”
32	“Urgent Care”
33	“Urgent Cares”
34	“Outpatient”
35	“Outpatients”
36	“Outpatient”
37	“Discharge, Patient”
38	“Discharges, Patient”
39	“Discharge Planning”
40	“Discharge Plannings"
41	25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40
42	24 AND 41

Appendix 2. Embase search (done on 18 September 2015)

1	Leukemia'/exp
2	Leukemia
3	1 OR 2
4	'Ambulatory care'/exp
5	'Ambulatory care'
6	'Outpatient care'/exp
7	'Outpatient care'
8	'Outpatient health service'
9	'Outpatient health services'
10	'Services, outpatient health'
11	'Clinic visits'
12	'Clinic visit'
13	'Urgent care'
14	'Urgent cares'
15	'Outpatient'/exp
16	'Outpatient'
17	'Outpatients'/exp
18	'Outpatients'
19	'Outpatient'/exp
20	'Outpatient'
21	'Discharge, patient'
22	'Discharges, patient'
23	'Discharge planning'/exp
24	'Discharge planning'
25	'Discharge plannings'
26	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25
27	**3 AND 26**

Appendix 3. Cochrane database (done on 14/Sept/2015)

1	Leukemia
2	Leucocythaemia
3	Leukemias
4	"Nonlymphoblastic, Acute"
5	acute leukemia
6	"Leukemia, Nonlymphocytic, Acute"
7	"Myeloblastic Leukemia, Acute"
8	"Acute Myeloblastic Leukemia"
9	"Myeloblastic Leukemias, Acute"
10	"Myelocytic Leukemia, Acute"
11	"Acute myelocytic leukemia"
12	"Myelogenous Leukemia, Acute"
13	"Nonlymphoblastic Leukemia, Acute"
14	"Acute Nonlymphoblastic Leukemia"
15	"Nonlymphoblastic Leukemias, Acute"
16	"Acute Myelogenous Leukemias"
17	"Myeloid Leukemia, Acute, M1"
18	"Leukemia, Myeloid, Acute, M2"
19	"Acute Myeloid Leukemia without Maturation"
20	"Leukemia, Biphenotypic, Acute"
21	"Leukemia, Myelogenous, BCR-ABL Positive"

22	"Precursor B-Cell Lymphoblastic Leukemia-Lymphoma"
23	“Precursor T-Cell Lymphoblastic Leukemia-Lymphoma”
24	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25	"Outpatient Care"[
26	"Ambulatory Care"
27	“Outpatient Health Service”
28	“Outpatient Health Services”
29	“Services, Outpatient Health”
30	“Clinic Visits”
31	“Clinic Visit”
32	“Urgent Care”
33	“Urgent Cares”
34	“Outpatient”
35	“Outpatients”
36	“Outpatient”
37	“Discharge, Patient”
38	“Discharges, Patient”
39	“Discharge Planning”
40	“Discharge Plannings"
41	25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40
42	24 AND 41

Appendix 4. Grey literature (done on 18/Sept/2015)

1	Leukemia
2	"Ambulatory care"
3	Outpatient
4	“Outpatient discharge"

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/16573