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Evidence-Based Guided Interventions in Acute Leukemia

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1. Introduction

Evidence based medicine (EBM) is becoming a cornerstone in the establishment of practical guidelines and is nowadays part of the process of decision making in medicine (Woolf 2000). In evidence based medicine, decision making is based on relevant clinical trials ranked by their relevance and validity according to established criteria. Indeed, well designed randomized controlled trials (RCTs) are considered the "gold standard". However, since hematological disorders such as acute leukemia are rare, RCTs with a large enough sample size are difficult to conduct.

Systematic reviews use a preplanned, explicit methodology to answer a predefined question and evaluate the benefit and harm of healthcare interventions. Meta-analyses quantitatively assemble results from RCTs to increase power when individual studies are too small to detect a statistically significant effect (Gale and Lazarus 2011). The quality of a systematic review reflects the quality of its included studies. Potential sources of bias are heterogeneity between the RCTs included, publication bias and difficulties in accessing data from the original clinical trials.

In this chapter we attempted to assemble the evidence on the available meta-analyses analyzing the data in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) patients. In certain domains, when no meta-analyses were identified, a literature search was performed and, if applicable, suggestions for future studies were made.

2. Methods

We searched The Cochrane and MEDLINE databases for systematic reviews. In Pubmed we crossed MeSH terms for 'acute myeloid leukemia' or 'acute lymphoblastic leukemia' with Clinical Queries to limit the search for systematic reviews.

We included systematic reviews of RCTs (with or without meta-analyses) assessing the effect of different chemotherapy regimens and supportive care on overall survival of patients with acute leukemia. We included the use of these treatment options in the following clinical settings: remission induction, post remission (consolidation) including autologous and allogeneic stem cell transplantation and maintenance.

We assessed the risk of bias in the systematic reviews by the following domains: use of explicit inclusion/exclusion criteria and a predefined protocol; comprehensive search;

whether selection bias was avoided; assessment of risk of bias of original trials; correct statistical methods to pool the data. Assessment of risk of bias in each of the systematic reviews based on the AMSTAR protocol is summarized in tables 1-2 and 4 (Liberati, *et al* 2009, Oxman and Guyatt 1991, Shea, *et al* 2007, Shea, *et al* 2009).

For the evaluation of prospective comparative trials in the transplantation field, we searched for meta-analyses including genetically randomized trials. These trials were defined by patient allocation to an intervention on the basis of sibling donor availability (donor group versus no-donor group) and were evaluated for potential bias as previously discussed (Ram, *et al* 2011).

3. An overview of systematic reviews in acute myeloid leukemia

Survival of AML patients has constantly been increasing from about 5-10% in 1975 to about 25% of diagnosed patients according to SEER data (1975-2007) in US population. This progress is the result of the progress in supportive care enabling treatment with intensive chemotherapy to induce remission and the use of allogeneic hematopoietic cell transplantation (HCT), as well as the use of prognostic factors in clinical decision making. For the majority of patients with AML this disease still has grave consequences. Our understanding of cytogenetic and molecular factors in the pathogenesis and the prognosis of patients with AML has evolved tremendously during the last decade. Still our ability to cure has remained unsatisfactory.

Treatment of AML with curative intent is generally divided into remission induction and post remission (also referred to as consolidation) courses (Dohner, *et al* 2010). Management of patients with AML depends mainly on their age, their response to therapy and the cytogenetic and molecular factors of the leukemic clone, stratifying patients into favorable, standard and unfavorable risk groups.

We herein reviewed the results of systematic reviews assessing chemotherapy for patients with AML. For each systematic review we evaluated the methodological quality using the AMSTAR assessment tool (Table 1).

3.1 Induction therapy

For more than 3 decades remission induction treatment consists of anthracyclines administered for 3 days and cytarabine given at a dose of 100-200 mg/m^2 in continuous infusion for 7 days. Efforts to improve response rate and survival of patients with AML included the addition of other chemotherapeutic drugs to the standard induction regimen, using different types and doses of anthracyclines, as well as different doses of cytarabine.

3.1.1 Does the type of anthracycline affect overall survival of adult patients with AML?

A systematic collaborative overview of individual patient data of RCTs that compared an idarubicin-based induction regimen with a different anthracycline-based regimen included trials from 1984 to 1993 including 1898 patients (AML Collaborative Group, 1998). Compared to daunorubicin, idarubicin improved remission rate (53% *vs.* 62%, respectively, p = 0.002) and overall survival (14% odds reduction, p = 0.03), however disease free survival (DFS) did not differ significantly (15% odds reduction, p=0.07). This overview fulfilled 4 of 11 criteria of the AMSTAR tool.

Since the publication of this systematic review new data has accumulated (Mandelli, *et al* 2009, Rowe, *et al* 2004).

3.1.2 Does the dose of anthracyclines during induction have an effect on survival?

Historically, the conventional induction anthracycline dose was the equivalent of daunorubicin 45-50 mg/m^2 daily given for 3 days. Large case series and observational studies supported a dose escalation to 60 mg/m^2. It remained questionable if the dose response curve has reached a plateau and whether the dose amplification benefit can be confirmed in RCTs. A few RCTs evaluated various dosages of anthracyclines. No published systematic review has summarized their findings so far.

Two RCTs evaluated dose intensification of anthracyclines (Fernandez, *et al* 2009, Lowenberg, *et al* 2009). Patients <60 years old treated with 90 mg/m^2 of daunorubicin, as compared with the standard 45 mg/m^2, achieved a higher rate of complete remission (CR) (70.6% *vs.* 57.3%; P<0.001) and a better overall survival (P=0.003) (Lowenberg, *et al* 2009). In another trial, >60 year-old patients treated with higher doses of daunorubicin, i.e. 90 mg/m^2 as compared to 45 mg/m^2 daily, for 3 days, had higher CR rates (64% for the high dose *vs.* 54% for the standard dose; P=0.002) (Pautas, *et al* 2010). There was no significant difference between the two groups in the incidence of hematological adverse events, 30-day mortality (11% and 12% in the 2 groups, respectively), or the incidence of adverse events (P=0.08). An overall survival benefit was demonstrated only in 2 subgroups: patients aged 60 to 65 years, and those with favorable cytogenetics. Paustas et al. compared 3-days of daunorubicin 80 mg/m^2/day with 3 or 4-days of idarubicin 12 mg/m^2/day in 468 patients aged 50 to 70 years. While a statistically significant higher rate of CR was demonstrated in patients treated with idarubicin (P = .04), there were no significant differences in the other outcomes.

Thus, conventional dose for remission induction in adult patients < 60 years with AML should be between 60 to 90 mg/m^2/day. There is no clear benefit for higher doses (90 mg/m^2/day) of daunorubicin compared to 45 mg/m^2 daily in adults >65 years.

3.1.3 Do higher doses of cytarabine during remission induction treatment improve survival?

Kern and Estey reviewed the literature to examine the effect of high dose cytarabine (≥1000 mg/m^2/dose) in induction therapy compared with standard dose (100-200 mg/m^2/day) cytarabine (Kern and Estey 2006). The search yielded 3 trials, evaluating 1691 adult AML patients < 60 years. There was no difference between high dose and standard dose cytarabine with regard to CR rate (relative risk 1.00; 95% CI 0.92 to 1.10) or early death rate (RR 1.53; 95% CI 0.84 to 2.78, random-effects model). However, 4-year overall survival was better in patients given high dose cytarabine (weighted mean difference, 6.211; 95% CI, 2.701 to 9.721). In this meta-analysis time to event data was analyzed as continuous data, the assumptions made for converting median to mean and their variance to standard deviation were not described, and weighted mean difference was used to pool results. This review fulfilled 7 of 11 criteria of the AMSTAR criteria.

3.2 Post remission therapy

3.2.1 What is the role of transplantation in patients with AML?

3.2.1.1 Autologous hematopoietic cell transplantation

Four systematic reviews evaluated the effect of autologous hematopoietic cell transplantation (HCT) in first CR (Ashfaq, *et al* 2010, Levi, *et al* 2004, Nathan, *et al* 2004, Wang, *et al* 2010).

Nathan et al. compared the efficacy of autologous HCT with chemotherapy (or no further treatment) in patients aged 15 to 55 years (Nathan, *et al* 2004). Their search yielded 6 trials including 1044 patients. Patients who underwent autologous HCT had a better DFS (probabilities ratio of 1.24, 95% CI 1.06 to 1.44) with similar long term mortality rate (RR 1.01, 95% CI 0.89 to 1.15). This review fulfilled 9 of 11 criteria of the AMSTAR tool. Levi et al performed a systematic review on the same question with similar findings (Levi, *et al* 2004).
A more recent systematic review included 12 RCTs (Wang, *et al* 2010). Patients treated with autologous HCT had lower relapse rate,better DFS, but no overall survival benefit probably because of higher treatment related mortality. Of note, at present, transplant related mortality is lower than the estimated 4% reported in these systematic reviews.

3.2.1.2 Allogeneic hematopoietic cell transplantation

Eight reviews and meta-analyses were identified but only three of them were systematic and comprehensive (Ashfaq, *et al* 2010, Hubel, *et al* 2011, Koreth, *et al* 2009). Koreth et al. performed a systematic review comparing allogeneic HCT with conventional consolidation chemotherapy or autologous HCT (Koreth, *et al* 2009). Patients allocated to the allogeneic HCT arm had an overall survival benefit (HR 0.90 95% CI 0.82 to 0.97, 15 trials), and relapse free survival (HR 0.80 95% CI, 0.74 to 0.86, 18 trials). In an analysis stratified according to the cytogenetic risk groups, only intermediate and poor risk AML patients allocated to the allogeneic HCT arm had improved overall survival, while favorable risk patients had similar overall survival in both allocated arms. This review fulfilled 10 of 11 criteria of the AMSTAR tool.
Another comprehensive systematic review (without a quantitative summary) was done through the National Institute for Health Research Health Technology Assessment (HTA) program in UK (Ashfaq, *et al* 2010). The results and conclusions of this very detailed review were consistent with those of the previous ones. Other systematic reviews were published earlier and were not as comprehensive (Oliansky, *et al* 2008, Schlenk, *et al* 2004, Visani, *et al* 2006, Yanada, *et al* 2005).

3.3 Consolidation – dose intensity of cytarabine

A systematic overview without a quantitative analysis of chemotherapy for patients with AML was conducted by The Swedish Council of Technology Assessment in Health Care (Kimby, *et al* 2001). In one trial consolidation was compared to no further treatment. This trial was closed early due to inferior remission duration in the latter group. In all the trials comparing high dose cytarabine to standard dose or maintenance therapy, high dose cytarabine was shown to be superior to the comparator, though overall survival advantage was not consistently shown. Consolidation with high dose cytarabine seemed to be of value mainly for patients with core binding factor AML and in younger patients, due to a high mortality rate in patients older than 60 years. This overview fulfilled 1 of 10 criteria of the AMSTAR tool.

3.4 Maintenance therapy instead of consolidation chemotherapy

This question was reviewed by Kimby et al. who found limited data to indicate that post-remission maintenance therapy with long-term attenuated chemotherapy can prolong remission duration compared to no further therapy (Kimby, *et al* 2001). However, the data in support of these conclusions are sparse and effect on survival was not shown.

3.5 Role of azacitidine

Azacitidine was not exclusively assessed in AML patients but rather analyzed in a pooled myelodysplasia/AML group of patients (20%- 30% blasts, defined by the WHO as AML)

Study ID by author year / AMSTAR criterion	The AML collaborative group 1998	Kern 2006	Nathan 2004	Levi 2004	Yanada 2005
Was an 'a priori' design provided?	Yes	Yes	Yes	Yes	Yes
Was there duplicate study selection and data extraction?	Not reported	Yes	Yes	Yes	No
Was a comprehensive literature search performed?	No	Yes	Yes	No	No
Was the status of publication used as an inclusion criterion? (i.e. grey literature was included)	Yes	Yes	No	No	No
Was a list of studies (included and excluded) provided?	No	No	Yes	No	Yes
Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes	Not reporte
Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	No	No	Yes	No
Were the methods used to combine the findings of studies appropriate?	Yes	No, analyzed survival data as a continuous variable	Unclear	Yes	Yes
Was the likelihood of publication bias assessed?	No	No	Yes	No	Yes
Were potential conflicts of interest included?	No	No	Yes	No	No
Total	5	6	8-9	6	5

Table 1. Assessment of risk of bias using AMSTAR criteria in systematic reviews in the field of AML

(Edlin, *et al* 2010). This RCT shows an overall survival benefit for azacytidine compared to best supportive care, low dose cytarabine, or intensive chemotherapy. Two RCTs that evaluated the effect of azacytidine in patients with high risk MDS (including patients with 20%- 30% blasts) showed improved time to transformation or death in patients given azacytidine (Fenaux, *et al* 2009, Silverman, *et al* 2002).

Azacytidine was also given as part of post remission chemotherapy: in the MRC AML 9 trial, patients given the azacitidine-chemotherapy arm as consolidation had fewer relapses comparedto patients given only chemotherapy ($p = 0.003$), but a higher treatment related mortality (4.5% vs. 0%), without a statistically significant improved long term survival (Rees, *et al* 1996).

In another trial, patients were randomized to post remission consolidation with different chemotherapy regimens: standard dose cytarabine-daunorubicin *vs.* the same treatment followed by amsacrine and azacytidine vs. thioguanine and standard dose cytarabine-daunorubicin (Volger, *et al* 1995). The 5-year DFS was 38%, 31%, and 27% ($p<0.05$), respectively.

4. Acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) is usually characterized by a specific gene rearrangement and the generation of the PML-RARα fusion transcript which results from a translocation between chromosomes 15 and 17. Targeted therapy with all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy results in cure in 70-80% of patients.

Two systematic reviews evaluated the first line treatment of patients with APL (Xu, *et al* 2009a, Xu, *et al* 2009b).

The first one includes 7 RCTs (392 patients) comparing ATRA plus arsenic trioxide to other treatments. Compared with arsenic trioxide monotherapy, arsenic trioxide plus ATRA affected neither CR or DFS rates nor mortality of relapsed APL patients. Arsenic trioxide plus ATRA improved CR rate, DFS, mortality rate and adverse reactions compared to the same regimen including also chemotherapy. The review fulfilled 6 of 11 criteria of the AMSTAR tool.

A systematic review and meta-analysis including 5 randomized controlled trials (328 patients) compared ATRA plus arsenic trioxide regimen with ATRA monotherapy in patients with APL showed an improved 2-year DFS rate in the group treated with ATRA arsenic trioxide.

5. An overview of systematic reviews in acute lymphoblastic leukemia

Acute lymphobIastic leukemia (ALL) is the most common acute leukemia in children, while the incidence is much lower in adults (National Cancer Institute. SEER Cancer Statistics Review Available at: http://seer.cancer.gov/csr/1975_2006). The outcome of pediatric ALL patients has evolved from an overall survival of less than 10% in the 1960s to approximately 80% at present (Pui, *et al* 2008). However, adult patients have a less optimistic prognosis. While the remission rate reaches 90%, the survival rate is only 40%-50% (Fielding 2008). ALL patients are stratified and treated according to algorithms that integrate the presenting features, leukemia features and early response to therapy (Faderl, *et al* 2003); However the classification to standard and poor risk disease varies among the major studies conducted in adult ALL patients (Hoelzer, *et al* 1988, Kantarjian, *et al* 2004, Lazarus, *et al* 2006, Le, *et al* 2006, Rowe, *et al* 2005, Ram, *et al 2010)*.

Treatment of adult ALL patients usually consists of remission induction and consolidation/intensification phases followed by either HCT or maintenance therapy.
As stated above, because the disease is relatively rare in adults, much of the knowledge and protocols have been adopted from pediatric regimens. Although we aim to focus on adult population, a portion of the data is based on evidence from pediatric trials.
For each systematic review we evaluated the methodological quality using the AMSTAR assessment tool (table 2).

5.1 Is there a specific induction regimen which is better?

Different groups use various induction regimens, which have not been compared head to head (Gokbuget and Hoelzer 2009, Kantarjian, *et al* 2004, Larson, *et al* 1995, Linker, *et al* 2002, Thomas, *et al* 2004b). In adult patients, the use of growth factors such as granulocyte colony-stimulating factor that accelerate hematopoietic recovery has greatly improved the success rate of ALL therapy (Kantarjian, *et al* 2004) and will be reviewed in a different part of this chapter.
One individual patient data meta-analysis examined the role of incorporating different types of anthracycines into pediatric induction regimens (CALLCG, 2009) and identified 4 trials recruiting 958 patients. They found that there was a borderline significant reduction in bone marrow leukemia relapse rate (OR 0.77, 95% CI 0.60 to 1.00; p=0.05) among patients treated with anthracyclines compared to those not, though there was no difference in non-bone marrow leukemia relapse rate (OR 0.88, 95% CI 0.63 to 1.25; p=0.5). The reduction in relapse rate translated into improved relapse free survival (OR 0.81; 95% CI, 0.66 to 1.00; p=0.05). However, event free survival (EFS) and overall survival were similar between the two groups. No significant differences in outcomes were demonstrated when different anthracyclines or when different adninistration schedules were compared. As this meta-analysis has been solely conducted in a pediatric population, results might not be applicable for adult patients. This systematic review fulfilled 5 of 11 criteria of the AMSTAR tool.

5.2 What is the role of pediatric inspired regimens for adult patients, mainly for the group of adolescents and young adults?

Several recent studies comparing the outcome of adolescents and young adults (AYAs) up to the age of 45 years, treated with pediatric versus adult protocols, demonstrated improved survival for AYAs who were treated by pediatric groups (Boissel, *et al* 2003, Ramanujachar, *et al* 2007, Stock, *et al* 2008). All are non-randomized trials and are therefore prone to significant bias. Thus, these trials are difficult to interpret because of the wide spectrum of patients' age, the small number of patients, the variations in the regimens utilized and the varying application of HCT in different studies. Recently our group completed a systematic review and meta analysis of all published comparative studies. We showed that up to the age of 20 years, pediatric inspired regimens are superior to conveintional afults chemotherapy (Ram, *et al* 2011). Currently there are several groups conducting prospective trials (e.g., US AALL0232) to further elucidate which is the best treatment for AYAs. Only then, solid conclusions to tailor the best treatment for AYAs should be drawn.

5.3 What is the role of thyrosine kinase inhibitors in the treatment of Philadelphia positive ALL?

Philadelphia positive ALL is a disease with a historically dismal prognosis in which HCT provided the only chance for cure (Fielding and Goldstone 2008). Recently, the introduction of tyrosine kinase inhibitors (TKIs) has opened wide new perspectives of how to treat these patients (Thomas, *et al* 2004a). We were not able to identify systematic reviews assessing the

	Induction Regimens	Role of post remission HCT					M
Study ID by author / AMSTAR criterion	CALLCG, BJH 2009	Ram, Cancer 2010	Yanada, Cancer 2006	Orsi, BMT 2007	Hahn, BBMT 2006	Ashfaq, Health Teq Asses 2010	CALLCG, Lancet 199
Was an 'a priori' design provided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there duplicate study selection and data extraction?	No	No	Yes	Yes	No	No	No
Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the status of publication used as an inclusion criterion? (i.e. gray literature was included)	No	Yes	Yes	No	No	No	No
Was a list of studies (included and excluded) provided?	No	Yes	No	Yes	No	Yes	No
Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes	Yes	Yes	No
Was the scientific quality of the included studies assessed and documented?	No	Yes	Yes	Yes	Yes	No	No
Was the scientific quality of the included studies used appropriately in formulating conclusions?	No	Yes	Yes	Yes	Yes	No	No
Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the likelihood of publication bias assessed?	No	Yes	No	Yes	No	No	No
Were potential conflicts of interest included?	Yes	Yes	No	No	No	Yes	No
Overall grading	5	10	8	9	6	6	3

Table 2. Assessment of risk of bias using AMSTAR criteria in systematic reviews in the field of ALL

role of the different tyrosine kinase inhibitors. Prospective comparison, for example, by using genetic randomization based on donor availability along with intention-to-treat analysis, is necessary to draw conclusions on the clinical utility of allogeneic HCT for these patients.

5.4 What is the role of allogeneic HCT in first CR?

Allogeneic HCT provides a potential curative approach for patients with ALL, mainly through the anti-leukemic effect of the graft. Nonetheless, the relatively high non-relapse mortality compared to other treatment options limits the widespread use of this approach (Hahn, *et al* 2006, Ram, *et al* 2011).

As stated in the Methods section, the preferred way to assess the role of allogeneic HCT is to use a genetic randomization design, allocating patients with a matched sibling donor and those lacking sibling donor to the donor/transplantation arm and the no-donor/alternative treatment arm, respectively (Ram, *et al* 2011).

Five systematic reviews were conducted (Ashfaq, *et al* 2010, Hahn, *et al* 2006, Orsi *et al* 2007, Ram, *et al* 2010, Yanada *et al* 2006), 3 out of which included also a meta analysis (Orsi *et al* 2007, Ram, *et al* 2010, Yanada *et al* 2006). All three meta-analyses showed that overall, for ALL patients achieving first CR, allogeneic HCT carries a survival benefit compared to the other options. While all 3 meta-analyses used similar search criteria, the strict intention to treat (ITT) inclusion criteria were different. Moreover, the two largest trials in the field (Cornelissen *et al* 2009, Goldstone *et al* 2008) were included only in the most recently published meta-analysis only (Ram, *et al* 2010). This meta-analysis included 10 genetically trials, randomizing 2,600 patients for the main comparison of allogeneic HCT vs. other treatments, with only seven trials, randomizing 1,863 patients, following strict ITT criteria (table 2). In this meta-analysis, survival benefit was statistically significant for the standard-risk patients (RR for all-cause mortality 0.80, 95% CI 0.68–0.94), while for the high-risk it it was not (RR 0.88, 95% CI 0.76–1.01) (Ram, *et al* 2010). As expected, there was a significant increase in non-relapse mortality in the allogeneic HCT arm (RR 2.99; 95% CI, 1.37-6.53) and a significant decrease in the relapse rate (RR 0.52; 95% CI, 0.33-0.83). This systematic review fulfilled 10 of 11 criteria of the AMSTAR tool.

Although a systematic review published by Yanada et al showed a similar survival advantage in favor of the donor group (HR 1.29, 95% CI 1.02 to 1.63, $p = 0.037$), superiority could be demonstrated for the high-risk patients subgroup only (HR 1.42, 95% CI 1.06 to 1.90; $p = 0.019$). This systematic review fulfilled 8 of 11 criteria of the AMSTAR tool.

The difference between the two meta-analyses might stem from two main causes: The first is the inclusion of the two recent large trials in the last meta-analysis only (Cornelissen *et al* 2009, Goldstone *et al* 2008) and the second from the different methodologies and inclusion criteria used in the various studies (with more emphasis on strict ITT methodology in the recently published meta-analysis).

Orsi et al. conducted an individual patient meta-analysis of four trials (Hunault *et al.*, 2004, Labar *et al* 2004, Ribera *et al* 2005, Thomas, *et al* 2004b). They also showed survival benefit for the donor group (mean EFS was 5.88 years in the donor group and 4.88 years in the no-donor group) with survival rate of 44.2% (± 2.9%) at 7 years in the donor group and 31.6% (± 2.2%) in the non-donor group, log-rank test p = 0.011. Performance of allogeneic HCT in first CR was found to be cost effective. This systematic review fulfilled 9 of 11 criteria of the AMSTAR tool.

To summarize, all meta-analyses suggest overall survival benefit for patients undergoing a matched donor allogeneic HCT in first CR when compared to other modalities. By drawing

firm conclusions based on strict ITT trials it is suggested that allogeneic HCT may be more effective for the standard risk group.

5.5 Is there a role for autologous HCT in first CR?

We identified three systematic reviews that reported on the comparison between post remission autologous HCT and maintenance chemotherapy (Ashfaq, *et al* 2010, Hahn, *et al* 2006, Ram, *et al* 2010). One of them also performed a meta-analysis of the available RCTs. Both Hahn et al. and Ashfaq et al. concluded that both autologous HCT and maintenance chemotherapy yield a similar outcome (Ashfaq, *et al* 2010, Hahn, *et al* 2006). They also suggested that autologous HCT might be a superior option for high risk patients. In the meta-analysis performed by our group (Ram, *et al* 2010), five conventionally randomized trials enrolling 963 patients were identified. Similar to previous systematic reviews, survival was comparable between the two arms (RR 1.02, 95%CI, 0.88 to 1.19) for both standard and high risk patients. However there was a significant increase in non-relapse mortality in the autologous HCT arm (RR 1.77; 95% CI, 1.12 to 2.8), though no statistically significant difference was demonstrated in the relapse risk (RR 0.92; 95% CI, 0.73-1.15).

	Yanada, Cancer 2006	Orsi, BMT 2007	Ram, Cancer 2010
*Bernasconi 1992**			+
*Sebban 1994**	+	+	+
*Attal 1995**			+
*Takeuchi 2002**	+		+
*Dombret 2002,Thomas 2004**	+	+	+
Labar 2004#	+		+
Hunault 2004#	+	+	+
*Ribera 2005**	+	+	+
*Vey 2006**			+
Cornelissen 2008#			+
*Goldstone 2008**			+
*Fielding, 2009**			+

*True ITT trial #Not strictly ITT trial – Reasons for the inability to perform ITT analysis: Labar,2004- inclusion of patients with no siblings in the non-donor arm; Hunault, 2004- inclusion of patients>50 years in the non-donor group ; Cornelissen,2008- inclusion of patients who underwent matched unrelated donor transplantation in the nondonor study arm

Table 3. Comparisons between 3 meta-analyses assessing the role of allogeneic hematopoietic cell transplantation in first complete remission

5.6 Which is the best maintenance therapy?

The post remission high relapse rate of adult ALL patients has encouraged the exploration of various post-remission modalities. The optimal type and duration of maintenance therapy and the value of further intensification are still debated.

We identified 3 relevant systematic reviews (CALLCG *et al* 1996, Eden, *et al* 2010, Escherich, *et al* 2011), reporting on pediatric patients.

The first, evaluating the impact of duration and intensity of the different maintenance regimens, included 16 trials, randomizing 746 patients (CALLCG et al., 1996) showed that maintenance treatment administered for up to 3 years was associated with a significantly lower relapse rate albeit a similar rate of death from leukemia. Of note, maintenance duration beyond 3 years did not yield any superiority . More intensive regimens were associated with significantly fewer relapse events and with prolonged survival (absolute difference in survival of about 3% at 5 years and of 4% at 8 years). This systematic review fulfilled 3 of 11 criteria of the AMSTAR tool.

The second systematic review evaluated the addition of steroids plus vincristine pulses during the maintenance period (Eden, *et al*). In an individual patient meta-analysis vincristine-prednisone pulses were shown to improves EFS (70.1% vs. 62% at 5 years; OR 0.71, 95% CI 0.61 to 0.84; p = 0.00004), while vincristine - dexamethasone pulses did not have this effect (80.9% vs. 79.9% at 5 year; OR 0.94; 95% CI, 0.8 to 1.11;p = 0.5) Overall survival was not affected by both combinations. (Bostrom, *et al* 2003). Results of this meta-analysis should be taken with caution as they might be significantly biased by different pre-maintenance induction regimens. This systematic review fulfilled 7 of 11 criteria of the AMSTAR tool.

The third systematic review compared between the various thiopurines (mainly thioguanine and metcaptopurine) as maintenance (Escherich, *et al*). In a meta-analysis of 3 trials, event-free survival was similar for the two agents (OR 0.89, 95% CI, 0.78 to 1.03). However in a subgroup analysis of males aged<10 years there was a significant benefit for thiogouanine in terms of EFS (OR 0.70, 95% CI, 0.58 to 0.84), although this did not result in a significant difference in overall survival (OR 0.83, 95% CI, 0.62 to 1.10). It was concluded that mercaptopurine, and not thiogouanine, should be the thiopurine drug of choice for maintenance. Although this conclusion is valid for pediatric patients, in the absence of data in adults this may also be applicable for them. This systematic review fulfilled 5 of 11 criteria of the AMSTAR tool.

5.7 What is the role of CNS prophylaxis and is there a "gold-standard" regimen?

CNS involvement at presentation in adult ALL patients is estimated as 5% (Lazarus, *et al* 2006). Nevertheless, without prophylaxis administration, CNS recurrence occurs in approximately 30% of adult patients in complete response (Omura, *et al* 1980). There are several options to administer CNS prophylaxis therapy. These include cranial radiotherapy and intrathecal or intraventricular chemotherapy.

One pediatric systematic review with individual patient meta-analysis (Clarke, *et al* 2003) reported that prophylactic radiotherapy reduced CNS relapse slightly more than long-term intrathecal therapy, however no survival benefit was shown. Also, higher than 21 Gy radiation dose did not correlate with lower relapse risk and, the addition of intravenous methotrexate to regimens containing either radiation and intrathecal therapy led to a better EFS. This systematic review fulfilled 4 of 11 criteria of the AMSTAR tool.

6. An overview of systematic reviews in supportive care for patients with acute leukemia

Supportive care in acute leukemia has improved dramatically during the last decades and contributed to the improved overall survival of AL patients.

7. Myeloid growth factors

The use of G-CSF and GM-CSF results in a dose dependent increase in the levels of circulating neutrophils, mainly as a result of shortening the transit time from stem cell to mature cells (Griffin 2001). During intensive chemotherapy, acute leukemia patients experience prolonged and profound neutropenia, which is a risk factor for bacterial and fungal infections, for increased mortality. Patients with acute leukemia can be treated with myeloid growth factors as primary or secondary prophylaxis (before or after the development of neutropenia, respectively) or for priming (before or concurrent with chemotherapy) with the aim of sensitizing blast cells and recruiting them into cell-cycle, thus enhancing their susceptibility to cytotxic agents like cytarabine.

Five systematic reviews assessed the effect of myeloid growth factors in acute leukemia patients.

The first one is a comprehensive systematic review and meta-analysis, published in 2007 by Sung et al and comprises 148 RCTs, randomizing 16,839 patients with all types of cancer. Patients were randomly assigned to receive chemotherapy with or without prophylaxis with myeloid growth factors (Sung, *et al* 2007). There was no difference between the two groups in short term all cause mortality and in infection related mortality. However, the use of myeloid-growth factors was associated with reduction of clinically and microbiologically documented infections (RR 0.75, 95% CI 0.62 to 0.92, and RR 0.86, 95% CI, 0.77-0.96, respectively). Subgroup analysis of acute leukemia patients did not show any difference in short term all cause mortality and infection related mortality, as well (Sung, *et al* 2007). This systematic review fulfilled 9 of 11 criteria of the AMSTAR tool.

The second systematic review and meta-analysis compared the prophylactic use of G-CSF in patients with AML receiving chemotherapy, to placebo/no treatment (control group) (Wang, *et al* 2009a, Wang, *et al* 2009b). This review included seven trials with almost 2000 participants, and did not show difference in overall survival between the G-CSF group and the control group (Wang, *et al* 2009a) This systematic review fulfilled 5 of 11 criteria of the AMSTAR tool.

In a systematic review and meta-analysis recently conducted by our group, we questioned the role of myeloid growth factors administrated to AML patients concurrent with or post chemotherapy (Gurion, *et al*., 2011). There was no difference in short term and long term all cause mortality, CR rate, DFS and relapse rate between the arm receiving growth factors and the control arm. Furthermore, the use of myeloid growth factors was not associated with a reduction in the incidence of infections. This systematic review fulfilled 10 of the 11 criteria of the AMSTAR tool.

Another recently published systematic review compared the administration of myeloid growth factors in AML patients receiving chemotherapy to control/placebo (Heuser, *et al* 2011). Among patients receiving primary prophylaxis, time to neutrophil recovery and hospitalization stay were shorter, yet no difference was shown in CR, event and DFS and overall survival, compared to no prophylaxis. Among patients receiving growth factors for priming, there was also no difference in CR, event free and disease free survival overall survival. This review fulfilled 7 of 11 criteria of the AMSTAR tool.

In another meta-analysis, the use of myeloid growth factors for priming did not affect CR rate, DFS or overall survival (Sung, *et al* 2009). Subgroup analyses according to type of myeloid growth factors, the timing of administration and patients' age did not affect

outcomes. The main limitation of these meta-analyses is their heterogeneity in terms of patients' characteristics, chemotherapy regimens and trial designs.
To conclude, the main beneficial effects of growth factors are acceleration of neutrophil recovery by 2 to 5 days and a reduction in the length of hospitalization.(Griffin 2001, Inoue, *et al* 1990, Lemoli, *et al* 1991, Lowenberg, *et al* 1988, Park, *et al* 1989). With regard to priming with growth factors in AML, 2 meta-analyses did not demonstrate a statistical significant effect on remission rate and overall survival and therefore do not support their regular use.

7.2 Prophylactic anti-infectious treatment

Two systematic review and meta-analyses assessed the effect of antibacterial and antifungal prophylaxis in neutropenic patients receiving chemotherapy.
Gafter-Gvili et al. evaluated the use of antibacterial prophylaxis for afebrile neuropenic patients (Gafter-Gvili, *et al* 2005). The administration of antibacterial prophylaxis reduced all-cause mortality by 33% (95% CI 0.55 to 0.81) in neutropenic patients who received any antibiotic prophylaxis and by 48% (95% CI 0.35 to 0.77) in patients who received quinolones for prophylaxis compared to placebo or no intervention. Also, the occurrence of febrile episodes and bacterial infections decreased significantly. This review fulfilled 10 of 11 criteria of the AMSTAR tool.
Robenshtock et al. evaluated antifungal agents for prophylaxis in neutropenic patients following chemotherapy or after allogeneic HCT (Robenshtok, *et al* 2007). All-cause mortality was reduced significantly in patients receiving antifungal prophylaxis compared with placebo, no treatment, or non-systemic antifungals (RR 0.84, 95% CI, 0.74 to 0.95). In a subgroup analysis of patients with acute leukemia there was a significant reduction in fungal-related mortality and documented invasive fungal infections, yet there was no difference in mortality. This review fulfilled 10 of 11 criteria of the AMSTAR tool.

7.3 Transfusion support

One systematic review and meta-analysis evaluated the prophylactic use of platelets in patients with hematological malignancies(Stanworth, *et al* 2004). Three studies compared prophylactic with therapeutic use of platelets. There was no difference in all-cause mortality, or mortality due to hemorrhagic cause. Of note, studies were conducted between 1974-1982 and were small with marked heterogeneity, thus the results of this meta-analysis should be taken with caution. Three prospective studies compared the platelet transfusion thresholds of 10 *vs.* $20x10^9$ /L. There were no statistically significant differences between the groups with regards to mortality, remission rates, number of participants with severe bleeding events or red cell transfusion requirements.
The main limitation of this review is the inclusion of a limited number of small studies in different three meta-analyses, carrying a potential risk for bias, though no publication bias was reported. This review fulfilled 8 of 11 criteria of the AMSTAR tool.
Recently, two published RCTs compared low dose to high dose prophylactic platelets transfusion (Heddle, *et al* 2009, Slichter, *et al*). Both showed no difference in grade 2-4 bleeding incidence between patients allocated to low threshold of platelets administration and no difference between different doses of platelet transfusion. However, one of the studies was prematurely stopped because of 5.2% grade 4 bleeding in the lower dose platelets compared to none in the high dose (Heddle, *et al* 2009).

Study ID by author / AMSTAR	Sung et al	Wang et al	Gurion et al	Heuser et al	Sung et al	Gafter et a
Was an 'a priori' design provided?	Yes	Yes	Yes	Yes	Yes	Yes
Was there duplicate study selection and data extraction?	Yes	No, not reported	Yes	Yes	Yes	Yes
Was a comprehensive literature search performed?	Yes No search in conference proceedings and in databases of ongoing trials	Yes No search in databases of ongoing trials	Yes	Yes No search in conference proceedings and in databases of ongoing trials	Yes No search in databases of ongoing trialV	Yes No search databases ongoing t
Was the status of publication used as an inclusion criterion? (i.e. grey literature was included)	No	No	No	Yes Unpublished trials were excluded	No	No
Was a list of studies (included and excluded) provided?	No, only a list of included studies was provided	No, only a list of included studies was provided	Yes	No, only a list of included studies was provide	No, only a list of included studies was provide	Yes
Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes	Yes	Yes
Was the scientific quality of the included studies assessed and documented?	Yes	No	Yes	No, only blindness was reported.	Yes, used Jadad scale for assessing quality	No
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	Yes	Not applicable	Yes	Yes
Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Was the likelihood of publication bias assessed?	Yes	R1	Yes	No	Yes	Yes
Were potential conflicts of interest included?	Yes	R1	Yes	Yes	No	Yes

Table 4. Assessment of risk of bias using AMSTAR criteria in systematic reviews of supportive care

8. Conclusions

The progress made in the last 4 decades in the treatment of patients with acute leukemia is the consequence of a constant process of testing, data compilation and re-testing. Data gathering on a specific question using explicit, preplanned scientific methods to identify select and synthesize all relevant studies is the process of systematic review, which provides the clinician with the best evidence, and should form the basis for rational medical decision-making.

In this chapter we examined the evidence accumulated in various aspects of leukemia management, based on RCTs and systematic reviews and meta-analyses. While in certain areas such as the role of tyrosine kinase inhibitors in Philadelphia positive ALL or allogeneic transplant in adult patients with ALL a consensus could be reached according to the data published so far, many questions are still open in the field of leukemia which warrant conduction of further clinical trials.

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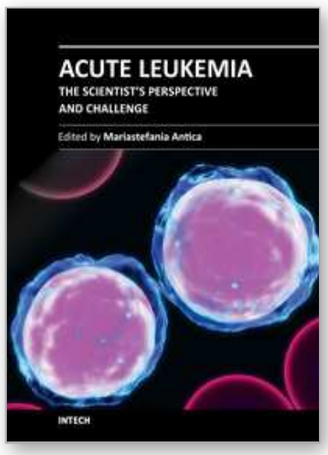

Acute Leukemia - The Scientist's Perspective and Challenge

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This book provides a comprehensive overview of he basic mechanisms underlying areas of acute leukemia, current advances, and future directions in management of this disease. The first section discusses the classification of acute leukemia, taking into account diagnoses dependent on techniques that are essential, and thankfully readily available, in the laboratory. The second section concerns recent advances in molecular biology, markers, receptors, and signaling molecules responsible for disease progression, diagnostics based on biochips and other molecular genetic analysis. These advances provide clinicians with important understanding and improved decision making towards the most suitable therapy for acute leukemia. Biochemical, structural, and genetic studies may bring a new era of epigenetic based drugs along with additional molecular targets that will form the basis for novel treatment strategies. Later in the book, pediatric acute leukemia is covered, emphasizing that children are not small adults when it comes to drug development. The last section is a collection of chapters about treatment, as chemotherapy-induced toxicity is still a significant clinical concern. The present challenge lies in reducing the frequency and seriousness of adverse effects while maintaining efficacy and avoiding over-treatment of patients.

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