

Acute Myeloid Leukemia

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Introduction

In the past decade cooperative groups in France, Germany, Scandinavia, the United Kingdom, and the United States have reported 5-year survival rates of 50% or better in children and adolescents with acute myeloid leukemia (AML). Marked intensification of cytotoxic chemotherapy, judicious use of bone marrow transplantation, and standardization of supportive care have each contributed to improved outcome. Although refractory or recurrent AML remains the principal cause of death, treatment-related mortality in phase III AML studies is higher than in any other paediatric neoplasm, ranging from 6% to over 15%. It is now possible to identify variables related to host, disease, and treatment that predict success or failure. These predictions have led to the risk-stratification of therapy in contemporary trials. At the same time there is emerging a vast array of pharmaceuticals, biologics, and vaccines designed for targets that are relatively AML specific. These new agents offer hope for more effective, less toxic therapy in the future. Introducing them into paediatric trials is a priority.

Treatment of AML

For many years paediatric AML therapy has relied on a chemotherapeutic backbone of cytarabine, anthracyclines and etoposide with or without marrow transplantation. Corticosteroids and thioguanine are included in some trials. The Medical Research Council (MRC) have developed a template based on a ten-day induction and post-remission therapy with 3 or 4 sequential combinations of high-dose cytarabine and alternating anthracyclines. The Children's Cancer Group (CCG) studies focus on intensive timing of 2 cycles of timed 5-drug induction and consolidation, followed by timed sequential high dose cytarabine or marrow transplantation. The Berlin-Frankfurt-Munster

(BFM) group uses an 8-day, 3-drug induction, high-dose cytarabine-based consolidation followed by a maintenance phase similar to paediatric ALL therapy and includes central nervous system prophylaxis often with cranial irradiation. Below we describe recent MRC and CCG studies and consider the role of marrow transplantation in first remission and the treatment of refractory and recurrent disease.

MRC-AML10 and MRC-AML12 studies

The survival of children with AML in the UK treated on MRC trials has improved dramatically over the past 30 years (*Fig 1*). MRC trials conducted in the 1980s suggested that increasing the intensity of induction and consolidation therapy might lead to an improvement in outcome and identified the best induction regime as DAT 3+10 (daunorubicin, ara-C, thioguanine) followed by a modified second course of DAT 3+8; two courses of DAT 3+10 having been shown to be too toxic.

MRC AML 10 (1988-1995)

1. Compared by randomization DAT 3+10 with ADE 3+10+5 (ara-C, daunorubicin, etoposide) as induction chemotherapy. These regimens delivered the same doses of daunorubicin and ara-C and therefore tested the comparative benefits of thioguanine and etoposide. There was no significant difference in CR rate (DAT 90% v ADE 93%), induction deaths (4%) or resistant disease (DAT 4% v ADE 3%). Overall survival, DFS, EFS were similar at 10 years (DAT 57% v ADE 51%, $p=0.3$; DAT 53% v ADE 48%, $p=0.3$; DAT 48% v ADE 45%, $p=0.5$ respectively). There was no evidence that children with monocytic involvement (FAB type M4 or M5) did better with an etoposide containing regimen, although this had previously been reported.

2. Investigated the role of BMT following 4 courses of intensive chemotherapy - DAT 3+10 or ADE 3+10+5, DAT 3+8 or ADE 3+8+5, MACE (amsacrine, ara-C, etoposide), MiDAC (mitoxantrone, high dose ara-C).

a) Children with a sibling donor were recommended for an allo-BMT in 1st CR; a genetic randomization. Analysed on donor availability ie intention to treat, allo-BMT was associated with a significant reduction in relapse risk from 45 % to 30% at 10 years ($p=0.02$), but this did not translate into a survival advantage (donor 68% v no donor 59%, $p=0.3$). The fewer relapses in the donor group were counter balanced by procedure related deaths (11%, $p=0.001$) and patients who relapsed after allo-BMT were not salvaged, whilst a percentage of those who had received chemotherapy alone were.

b) Children who did not have a donor were randomized to an A-BMT or no further treatment. Again at 10 years, there was no significant overall survival advantage for A-BMT (A-BMT 70%v NFT 58%, $p=0.2$), but there was a decrease in the relapse risk (A-BMT 31% v NFT 52%, $P=0.03$) and a significant improvement in DFS (A-BMT 68% v NFT 44%, $p=0.02$). The reduction in the relapse risk did not translate into a significant improvement in overall survival because children who relapsed and who had not had an A-BMT were more likely to be salvaged with second line treatment than those who had had an A-BMT.

Therefore MRC AML 10 failed to show a survival advantage for either allo-BMT or A-BMT in 1st CR, although both were associated with a reduction in the relapse risk. The failure to translate this into an improvement in overall survival differed by type of transplant.

3. AML 10 allowed stratification of patients into good, standard and poor risk groups based on their cytogenetics and response to the first course of treatment. Good risk patients are those with favourable genetic abnormalities – t(8,21), t(15,17), inv(16) irrespective of their

bone marrow status after course 1 of therapy. Standard risk patients are those with neither favourable or adverse cytogenetic abnormalities and not more than 15% blasts in their bone marrow after course 1 of therapy. Poor risk patients are those with more than 15 % blasts in their bone marrow after course 1 of therapy and adverse genetic abnormalities - -5, -7, del(5q-), abn (3q), complex karyotype (>/- 5 abnormalities).

Survival from 1st CR for these risk groups was 77%, 58% and 30% respectively and relapse rates 35%,43% and 72% (both $p<0.0001$) at 10 years.

MRC AML 12 (1995-2002)

This trial took forward the marginally better induction regimen from MRC AML 10 (ADE-when paediatric and adult results were combined) and the standard MRC template became ADE, ADE, MACE, MiDAC.

1. MAE (mitoxantrone, ara-C, etoposide) was compared to ADE; mitoxantrone being potentially less cardiotoxic than daunorubicin. The CR rates are similar (ADE 92% v MAE 90%) and the estimated probability for 5-year survival is not significantly different (ADE 64% v MAE 70%, $p=0.1$).

2. The reduction in relapse risk, similar for A-BMT and allo-BMT, in AML 10 suggested that the benefit might be one of an additional block of treatment rather than a graft versus leukaemia effect. The benefit of additional treatment was tested by the introduction of a fifth course of therapy in a randomized fashion. HD ara-C with asparaginase was chosen to avoid further anthracycline exposure. To date there is no benefit for an additional block of treatment suggesting that the ceiling of benefit for chemotherapy may have been reached with four blocks of treatment although the results of this trial are immature and follow-up continues.

3. Treatment was stratified by risk group. The risk group stratification derived from MRC AML 10 remains prognostically significant in MRC AML 12.

4. Good risk patients were not eligible for BMT in first CR, but standard and poor risk patients were. Although no benefit in OS had been

demonstrated for allo-BMT in AML 10, other co-operative groups reported benefit, and it seemed reasonable to continue to investigate the role of allo-BMT. A-BMT was not employed in AML 12 in the absence of a demonstrable benefit in OS and because of its potential long-term morbidity. When results from MRC AML 10 and 12 are combined, they show a significant reduction in relapse risk ($2p=0.02$), which does not translate into a significant reduction in DFS ($2p=0.06$) or OS ($2p=0.1$)

5. At present the results of MRC AML 12 are superior to MRC AML 10. The estimated probability of 5 year OS, EFS, DFS are 66%, 56% and 61 % respectively.

CCG-2891, CCG-1941, and CCG 2961 studies

In the 1980s and early 1990s conventional induction therapy involved 7 days of chemotherapy, a week of rest, and examination of the marrow on day 15 to assess efficacy: if there was residual leukemia, therapy was repeated; if there was <5 percent blasts, therapy was delayed until recovery of trilineage hematopoiesis. CCG-2891 (1989-1994) tested 2 hypotheses: 1) compared to conventional induction, an intensively-timed induction would more effectively reduce the leukemic population; and 2) that matched related donor bone marrow transplantation (MRD BMT) would achieve higher disease-free survival and overall survival than either purged autologous marrow transplantation (ABMT) or high-dose ara-C based chemotherapy. Intensive timing induction consisted of dexamethasone, cytarabine, thioguanine, etoposide and daunomycin (rubidomycin) (DCTER) given over 4 days, rest for 6 days, and repetition of the same drugs on day 11 regardless of marrow status and patient condition. A second course of the same therapy was repeated in phase 2. In Phase 3 patients with matched related donors underwent BMT and those without donors were randomly assigned to ABMT or chemotherapy. Intensive timing consisted of dexamethasone, cytarabine, thioguanine, etoposide and daunomycin (rubidomycin) (DCTER) given over 4 days, rest for 6 days, and repetition of the same drugs on days 11 through 14. regardless of marrow status and patient condition.

Excluding patients with Down syndrome, acute promyelocytic leukemia, myelodysplastic syndrome and secondary AML, 318 patients were randomized to conventional timing and 556 received intensive timing, 299 of whom received granulocyte-colony –stimulating factor starting on day 6. Treatment-related mortality in 2 courses of induction was 4% with standard timing, 13% with intensive timing ($p=0.05$) and 8% with intensive timing plus G-CSF; respective induction failure was 23%, 10% and 10%. Despite a significantly higher induction mortality, intensive timing effected a significantly higher EFS (44+4% vs. 27 +5%), DFS (60+4% vs. 37+5%) and OS (49+4% vs. 34+5%) at 9 years from on study.

In CCG-2891 MRD BMT was significantly better than either ABMT or chemotherapy. Patients DFS and OS of patients who received intensive timing induction was consistently superior to that of standard timing in all 3 post-remission regimens implying that better induction breeds post-induction results. EFS and OS with and without G-CSF were nearly identical.

CCG-2891 demonstrated that despite a significantly higher induction mortality, intensive timing effected a significantly higher EFS and OS. In this study MRD was significantly better than either ABMT or chemotherapy. Patients DFS and OS of patients who received intensive timing induction was consistently superior to that of standard timing in all 3 post-remission regimens implying that better induction gives rise to better post- induction results.

CCG-2941 (1994-1996) was a pilot study to test feasibility of replacing 4 mg of daunorubicin with 1 mg idarubicin (IdaDCTER) and eliminating 3 cycles of lower dose chemotherapy used in CCG-2891. After enrollment of 60 patients, interim analysis showed a 12 percent toxic mortality and 20 percent withdrawal. The replacement of daunorubicin with idarubicin on days 1-4 and 11-14 was deemed unfeasible in the intensive timing paradigm. The second idarubicin was replaced by daunorubicin and achieved a toxicity profile similar to that of daunomycin alone in CCG-2891.

CCG-2961 (1996-2002) used the Idarubicin/daunorubicin induction in all patients. It tested the hypothesis that changing the Phase II

consolidation therapy to a potentially non-cross-resistant combination, fludarabine, cytarabine, idarubicin, would achieve higher DFS and OS and that administering Interleukin-2 after high-dose cytarabine intensification would recapitulate the effects of graft-vs-leukemia of MRD BMT. The study was suspended in 1999 because of a projected treatment-related mortality in excess of 12%. It was reopened after 9 months with mandated standardized supportive care guidelines.

Among 900 patients with de novo AML, remission induction rate was 87%; OS, 53+3%, and EFS is 44+3%, at 3 years. The biggest difference in this study occurred in the comparisons of the 495 patients enrolled prior to suspension and the 404 enrolled after suspension: EFS 41+4% vs. 47+5% OS 52+5% and 63+5% ($p=0.003$) pre and post-suspension respectively. ($P=$).

Bone marrow and stem cell transplantation in first remission

There is considerable debate concerning which patients should receive MRD BMT in 1st CR. While trials in the United States and France have demonstrated that compared to intensive chemotherapy or ABMT, MRD BMT significantly improves EFS and OS, the MRC AML-10 and the BFM 93 trial in Germany have not shown a statistically significant advantage to MRD BMT. The combined paediatric and adult experience in MRC AML10 demonstrated a significant benefit to ABMT compared to no further therapy after 4 courses of intensive chemotherapy, which emerged late at two years. These discordant results may arise from the differences in patient populations and treatment protocols of each cooperative group, the statistical limitations of relatively small numbers, and the biases of parents, guardians and physicians regarding post-induction therapies. As of 2005, a consensus is emerging that MRD BMT in 1st CR is unnecessary for paediatric patients with AML with the cytogenetic abnormalities $t(15;17)$, $t(8;21)$, and $(inv\ 16)$. In most recent studies, transplant-related mortality for MRD in 1st CR is <10 per cent, but some survivors have graft vs. host disease, and almost all are infertile. Patients who receive chemotherapy only do not have these problems. Some paediatric groups favor busulfan and cyclophosphamide cytoreduction

rather than total body irradiation (TBI) plus an alkylating agent; however, it is not clear that cytoreduction with chemotherapy only is either less toxic or more or less efficacious than TBI.

Refractory and Recurrent AML

Refractory disease and relapse remain the major causes of treatment failure in AML. Patients with refractory disease or with relapse occurring within a year from diagnosis of AML have a poor prognosis: less than 20 percent of patients survive 2 years. High dose cytarabine with an anthracycline other than that used previously is the most common salvage regimen. In most cases once remission is achieved stem cell transplantation is considered the treatment of choice. Since many patients with matched related donors have already had a MRD BMT, the majority of patients received transplants from alternative donor sources. If there is no matched related donor, MUD transplant, or in younger, smaller patients, cord blood transplant may be an accessible alternative. Most cytoreduction in the setting of relapse includes TBI. Treatment-related mortality with alternative donors is 20-30%. Recent studies in adults are demonstrating some success with the non-myeloablative stem cell transplantation using low-dose (200cGy) TBI and cytoreduction that includes fludarabine monophosphate; whether this will be superior to myeloablative transplantation remains to be seen. Recently, new biologic therapies that may be more effective and less toxic have been introduced into AML therapy. Gemtuzumab ozogamicin, an anti-CD-33 antibody linked to calicheamicin, has sometimes induced complete remissions in recurrent adult and paediatric AML. Inhibitors of farnesyl transferase an enzyme involved in RAS activation have had activity in unfavorable AML in older adults and in juvenile myelomonocytic leukemia in infants. Vaccines targeting WT1, the Wilms tumor gene, telomerase, surviving, and homeobox genes have shown efficacy in preclinical trials. Many of these agents are expected to be most useful in early remission, in the setting of minimal residual disease.

Most relapses are marrow relapses. There is no standard approach to management of extramedullary relapses. There are reports of occasional control with local treatment only. However, in most cases extramedullary relapse

is a harbinger of marrow relapse. The role of local irradiation, new systemic therapy, and stem cell transplantation remain to be defined.

Prognostic Factors And Risk-Stratification

1. The Host

Table 1 lists factors related to host, disease and treatment that are predictive of outcome. Among the host-related factors, genetic predisposition to AML probably has the most profound impact on outcome. There is general agreement the patients with Down Syndrome (DS) or Down Syndrome mosaicism under 5 years of age have a significantly better outcome than other patients with AML. In DS, AML typically takes the form of a megakaryoblastic leukemia that is especially sensitive to cytarabine. Patients with DS are often treated according to separate protocols that are substantially less intensive than contemporary AML phase III trials. In contrast, patients with germline marrow failure syndromes such as Fanconi anemia, Kostmann syndrome, and Shwachmann-Bodian-Diamond syndrome are excluded from the phase III trials because they cannot tolerate therapy with anthracyclines and alkylating agents, and they do not have the ability to restore trilineage hematopoiesis following therapy. Transplantation with reduced-intensity cytoreduction before occurrence of AML is the treatment of choice.

Age is also an important prognostic factor with younger being better. About 10 percent of neonates with Down syndrome have a transient megakaryoblastic leukemic disorder that in most cases regresses spontaneously; in up to a third it recurs in later infancy as the favorable form of megakaryoblastic leukemia described above. Occasionally AML in genotypically normal neonates regresses spontaneously. When DS infants are excluded in most studies outcomes of the remaining infants are similar to those of children over age 2 years.

As a group children fare better than adolescents, and in the MRC studies, children and adolescents had significantly better outcomes than adults under age 45 years. In most studies there is no significant difference in outcomes of males and females. In the CCG studies black patients experience a significantly inferior EFS and OS compared to white patients; ethnicity has

not been addressed in most other studies. Also in the CCG studies, presence of a matched family donor is associated with better outcomes.

2. The Disease

Factors related to disease are white blood cell count at diagnosis, extramedullary disease, FAB morphology, immunophenotype, cytogenetics and most recently a few molecular markers. A white blood cell count under 20,000/mm³ is generally favorable and over 100,000 is unfavorable. Isolated chloromas were favorable in CCG-2891; patients without clinically detectable marrow disease require systemic therapy. The impact of CNS disease at diagnosis is variable.

The impact of FAB subtype varies from study to study. Megakaryoblastic leukemia, FAB M7 or erythromegakaryoblastic leukemia (FAB M6/M7) in patients who do not have Down syndrome generally has a poorer outcome than the other FAB types. Early BFM studies noted that eosinophilia was favorable, but this may reflect overlap between the FAB M4 eo phenotype and the inversion 16 genotype.

Blasts from over 90 percent of paediatric patients with AML express one or more myeloid-associated surface antigens CD13, CD14, or CD33; 30 percent of cases show expression of B-lymphocyte antigens, 60 percent express T-lymphocyte antigens. Expression of lymphoid-related antigens is of no prognostic significance. There is no consensus about favorable or unfavorable immunophenotype. Expression of combinations of antigens is highly patient specific and can be used to monitor minimal residual disease.

In over 70 percent of cases AML, the blasts have an abnormal karyotype. There is some overlap between immunophenotype, morphology, and cytogenetic findings. CD19⁺ and CD56⁺ are associated with FAB AML M2/t(8;21); CD2⁺ and CD7⁺ with FAB AML M2/t(8;21 negative); and CD33⁺, CD34⁻ with FAB AML M3/t(15;17). In these cases it is the cytogenetic marker that determines outcomes. There is now general agree t(8;21), inv(16), and t(15;17) are relatively favorable subtypes. Patients with t(15;17) have acute promyelocytic leukemia (APL). In many cooperative groups, patients with APL are treated with combinations that emphasize all-trans

retinoic acid and anthracyclines. APL is also particularly sensitive to gemtuzumab, azotamycin and arsenic trioxide. In both paediatric and adult studies monosomy 7 or 7q- genotype is associated with poor outcome. Retrospective studies show that allogeneic stem cell transplantation is the treatment of choice, but there are no studies that allocate these patients to alternative donor transplants in first remission.

There are many studies in AML in adults and several in paediatrics that show that internal tandem duplication of the receptor for FLT3 ligand (FLT3 ITD) is associated with a poor outcome. This is the only molecular marker for which the results are consistent across all studies. Overexpression of P glycoprotein has been associated with multiple drug resistance in vitro and in vivo. However, results of clinical trials are mixed, and inhibiting p glycoprotein has not resulted in significant improvements in AML.

3. The Treatment

Treatment is obviously an important variable: with the exception of AML in some neonates, without treatment AML is fatal and randomized studies indicate that some treatments are better than others. How rapidly the treatment reduces the burden of leukemia is an important predictor of outcome. Standard measures of response are the blast percentage on the day 15 marrow and achievement of remission after one or two courses of therapy. A day 15 marrow with less than 5 percent or less than 15% blasts portends a higher probability of survival. Failure to reduce the blast percentage to <5% and regenerate trilineage hematopoiesis after the first course of therapy predicts a relatively high probability of treatment failure. However, the majority of patients who experience relapse are in neither of these groups; hence more sensitive indicators of residual disease are needed. Multichannel flow cytometric assessment of marrow to detect 0.1% residual blasts at the end of induction identifies a larger population of patients at risk for relapse. PCR-based analyses are suitable for detection of 0.01% to 0.0001% residual blasts. However, rare blasts with t(8;21) are present in the majority of patients who are in remission and remain in remission for years. In this case an increase in the numbers of PCR-detected cells may predict future relapse.

Another parameter of treatment is supportive care. In both the MRC 10 and CCG-2961 studies implementation of standardized supportive care guidelines reduced the treatment-related mortality. It is likely that experience with a protocol is important as well. In CCG-2961 the mortality was reduced and EFS and OS improved after the first 18 months before the institution of mandatory guidelines. The improvement could not be accounted for solely by reduction in mortality but may include nuances in care that reduce morbidity as well.

Conclusion

The outlook for children with AML continues to improve. Similar and encouraging results have been obtained by a number of co-operative groups provided that intensive regimens with anthracyclines and HD ara-C are used. MRC results suggests that there may be a ceiling of benefit from chemotherapy and that further improvement in leukaemia control will be dependent on alternative approaches. The benefit of A-BMT is probably at best that of additional treatment. The role of allo-BMT in 1st CR continues to be tested. However, as the results from intensive chemotherapy continue to improve, the potential benefit of allo-BMT may become more limited and restricted to certain groups of patients, particularly alternative donor transplant. Monoclonal antibodies, drugs targeted at specific fusion genes and multi-drug resistance modifiers are being tested. Trials combining Gemtuzumab with intensive chemotherapy are ongoing. Toxicity can be limited by restricting transplantation and reducing anthracycline exposure where appropriate.

Risk group stratification will allow the targeting of therapy to risk. Cytogenetics and the speed of response to treatment have already been identified as prognostically significant. MRD monitoring, gene expression profiling and the identification of additional prognostic indicators eg FLT 3 may further define risk. The low CNS relapse rate in AML with intrathecal CNS directed treatment alone challenges the use of cranial irradiation with its long-term sequelae. Finally, AML is a heterogeneous disease with a number of rare subtypes, the treatment of which can only be addressed by international collaboration.

Table : Factors Predictive of Outcome in Paediatric AML

	Favorable	Unfavorable
The Host		
<i>Genetic</i>		
Down Syndrome	••••	
Fanconi anemia		•••
Shwachmann-Diamond		•••
Kostmann Syndrome		•••
Matched related donor	••	
<i>Age</i>		
Infant	••	
Child	••	
Adolescent		••
<i>Ethnicity</i>		
White	••	
Black		••
Hispanic		••
<i>Body Mass Index</i>		
Normal (10-95 %)		
Underweight (<10 %)		••
Obese (> 95 %)		••
Disease		
<i>White Blood Cell Count</i>		
<20,000/mm ³		••••
>200,000/mm ³		••••
<i>Morphology</i>		
M7, M/67		••
<i>Cytogenetics</i>		
del (7), 7q-		••••
t(8;21)	•••	
t(15;17)	••••	
inv(16)	••••	
complex karyotype		••••
<i>Molecular genetics</i>		
FLT3 ITD		••••
P-glycoprotein expression	•	
Treatment		
Early Response	••••	
Induction Failure		••••

Legend: Each • corresponds roughly to the level of evidence and the strength of agreement in the paediatric oncology community.

Reviews of CCG/COG and MRC Trials in Paediatric AML

1. Hann IM, Webb DK, Gibson BE, Harrison CJ. MRC trials in childhood acute myeloid leukaemia. *Ann Hematol.* 83 Suppl 1:S108-12. 2004;
2. Woods WG. Intensified induction therapy for children with AML. *Ann Hematol.* 83 Suppl1: S119-20. 2004.

Induction Therapy

1. Hann IM, Stevens RF, Goldstone AH, et al. Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia. Results of the Medical Research Council's 10th AML trial (MRC AML10). Adult and Childhood Leukaemia Working Parties of the Medical Research Council. *Blood* 89(7):2311-8, 1997.
2. Woods WG, Kobrinsky N, Buckley J, et al. Timed sequential induction therapy improves post-remission outcome in acute myeloid leukemia: A report from the Childrens Cancer Group. *Blood* 87(12): 4979-4989, 1996.
3. Lange BJ, Dinndorf P, Smith FO, et al. Pilot study of idarubicin-based intensive timing induction therapy for children with previously untreated acute myeloid leukemia in Children's Cancer Group (CCG) Study 2941. *J Clin Oncol* 22:150-156, 2004.

Post-Remission Therapy

1. Stevens RF, Hann IM, Wheatley K, Gray RG. Marked improvements in outcome with chemotherapy alone in paediatric acute myeloid leukemia: results of the United Kingdom Medical Research Council's 10th AML trial. MRC Childhood Leukaemia Working Party. *Br J Haematol.* 101:130-40. 1998.
2. Woods WG, Neudorf S, Gold S., et al. A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation and aggressive chemotherapy in children with AML in remission: A report from the CCG. *Blood*;97:56-62, 2001
3. Watson M, Buck G, Wheatley K, Homewood JR; et al. UK Medical Research Council AML 10 trial. Adverse impact of bone marrow transplantation on quality of life in acute myeloid leukaemia patients; analysis of the UK Medical Research Council AML 10 Trial. *Eur J Cancer.* 40(7):971-8. 2004
4. Neudorf S, Sanders J, Korbrinsky N, Alonzo TA, et al. Allogeneic bone marrow transplantation for children with acute myelocytic leukemia in first remission demonstrates a role for graft versus leukemia in the maintenance of disease-free survival. *Blood* 2004;103: 3655-61.
5. Alonzo TA, Wells RJ, Woods WG, et al. Postremission therapy for children with acute myeloid leukemia. The Children's Cancer Group experience in the transplant era. *Leukemia* 19: 965-70, 2005.

Prognostic Factors

1. Grimwade D, Walker H, Oliver F, Wheatley K, Harrison C, Harrison G, Rees J, Hann I, Stevens R, Burnett A, Goldstone A. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. *Blood.* 92. 2322-33, 1998.

References

2. Wheatley K, Burnett AK, Goldstone AH, Gray RG, Hann IM, Harrison CJ, Rees JK, Stevens RF, Walker HA simple, robust, validated and highly predictive index for the determination of risk-directed therapy in acute myeloid leukaemia derived from the MRC AML 10 trial. United Kingdom Medical Research Council's Adult and Childhood Leukaemia Working Parties. *Br J Haematol.* 107:69-79, 1999.
3. Meshinchi M, Woods WG, Stirewalt DL, et al. Prevalence and prognostic significance of FLT3 internal tandem duplication in paediatric acute myeloid leukemia. *Blood.*;97:89-94, 2001.
4. Kottaridis PD, Gale RE, Frew ME, Harrison G, et al. The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. *Blood.* 98:1752-9, 2001.
5. Davies SM, Alonzo TA, Lange BJ, Aplenc R, Smith FO, Ross JA, Perentesis JP, Woods WG. Reduced survival in black children with acute myeloid leukemia: a Children's Cancer Group Study. *Blood* 100:122. ASH December 2002.
6. Sievers EL, Lange BJ, Alonzo TA, et al. Immunophenotypic evidence of occult leukemia during remission predicts relapse: results from a prospective Children's Cancer Group study of 252 acute myeloid leukemia patients. *Blood*; 101:3398-406, 2003.
7. Dusenbery KE, Howells WB, Arthur DC, et al. Extramedullary Leukemia (EML) in Paediatric Patients with New Diagnosed Acute Myeloid Leukemia: A Report from the Children's Oncology Group (CCG). *JPHO* 25:760-768, 2003.

Relapse

1. Dinndorf PA, Avramis VI, Wiersma S, et al. Phase I/II study of idarubicin given with continuous infusion fludarabine followed by continuous infusion cytarabine in children with acute leukemia: a report from the Children's Cancer Group. *Clin Oncol.* Aug;15(8):2780-5. 1997.
2. Webb DK, Wheatley K, Harrison G, Stevens RF, Hann IM. Outcome for children with relapsed acute myeloid leukaemia following initial therapy in the Medical Research Council (MRC) AML 10 trial. MRC Childhood Leukaemia Working Party. *Leukemia*;13:25-31, 2001.
3. Wells RJ, Adams MT, Alonzo TA, et al. Mitoxantrone and cytarabine induction, high-dose cytarabine, and etoposide intensification for paediatric patients with relapsed or refractory acute myeloid leukemia: Children's Cancer Group Study 2951.; Children's Cancer Group Study 2951. *J Clin Oncol*;21:2940-7, 2003.
4. Arceci RJ, Sande J, Lange B, et al. Safety and efficacy of gemtuzumab ozogamicin (Mylotarg) in paediatric patients with advanced CD33-positive acute myeloid leukemia. *Blood* epub May 10 2005.

Treatment Related Mortality and Supportive Care

1. Riley LC, Hann IM, Wheatley K, Stevens RF. Treatment-related deaths during induction and first remission of acute myeloid leukaemia in children treated on the Tenth Medical Research Council acute myeloid leukaemia trial (MRC AML10). The MCR Childhood Leukaemia Working Party. *Br J Haematol.* 1999 Aug;106(2):436-44.
2. Alonzo, TA, Kobrinsky NL, Aledo A, et al. The Impact of Granulocyte Colony-Stimulating Factor Use During Induction for Acute Myelogenous Leukemia in Children: A Report from the Children's Cancer Group. *JPHO*;24:627-35, 2003.
3. Lange BJ, Gerbing RB, Feusner J, Skolnik J, Sacks N, Smith FO, Alonzo TA. Mortality in overweight and underweight children with acute myeloid leukemia. *JAMA* 2005;293:203-211.