Greater Manchester and Cheshire Cancer Network

Guidelines for the management of Acute Myeloid Leukaemia

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Contents

1. Network guidelines introduction

These guidelines were drafted and agreed by the GM&C network working group for AML. They have in part been derived from the current BCSH guidelines on the management of AML in adults, further developed to incorporate recent clinical data and trials- to be specifically relevant for the GM&C Cancer Network.

Appropriate setting for therapy

Recent recommendations from the National institute for Clinical Excellence should be followed (http://www.nice.org.uk). Patients should be managed by a multi-disciplinary team serving a population of at least 500,000, with induction therapy only carried out in centres treating at least five patients per year with induction chemotherapy with curative intent.

Adolescent patients

All patients aged 16-18 should be referred to the regional adolescent unit at Christie NHSFT for management, patients aged 19- 24 should be made aware of the adolescent facility at diagnosis although may elect for shared care, or for their primary treatment centre to be at another level 2 unit.

2. Diagnosis of Acute Myeloid Leukaemia

2.1 Classification

The World Health Organisation (WHO) System For The Diagnosis And Classification of AML (Jaffe et al 2001) superseded the modified FAB classification (Bennett et al 1985) and its use was proposed in the 2006 BCSH guidelines (Milligan et al 2006) Significant changes to the FAB classification were

1. Reducing the marrow blast percentage separating Myelodysplasia from AML to 20% from 30%
2. Taking account of preceding MDS or myeloproliferative disorders
3. Using categories defined by specific cytogenetic abnormalities or equivalent molecular abnormalities
4. Taking account of multilineage dysplasia with or without a preceding marrow disorder
5. Recognising previous cytotoxic chemotherapy as part of the classification
6. The introduction of new morphological subtypes

The WHO System has subsequently been revised (Vardiman et al 2009).The most significant changes being

1. AML with recurrent genetic abnormalities
    a. As in the previous edition, AML with t(8;21)(q22;q22), inv(16)(p13.1q22) or t(16;16)(p13.1;q22), and APL with t(15;17)(q22;q12) are considered as acute leukemia regardless of blast count in the PB or BM, but in contrast to the previous edition, for AML with t(9;11)(p22;q23) or other 11q23 abnormalities, as well as for all other subgroups (except the rare instance of some cases of erythroleukaemia) blasts of 20% or

more of white blood cells in PB or of all nucleated BM cells is required for the diagnosis of AML.

b. In APL with t(15;17)(q22;q12); *PML-RARA*, variant *RARA* translocations with other partner genes are recognized separately; not all have typical APL features and some have all-*trans* retinoic acid (ATRA) resistance.
c. The former category, AML with 11q23 (*MLL*) abnormalities has been redefined to focus on AML with t(9;11)(p22;q23); *MLLT3-MLL*. Translocations of *MLL* other than that involving *MLLT3* should be specified in the diagnosis. Other abnormalities of *MLL*, such as partial tandem duplication of *MLL* should not be placed in this category.
d. Three new cytogenetically defined entities are added: (1) AML with t(6;9)(p23;q34); *DEK-NUP214*, (2) AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*; and (3) AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*.
e. Two provisional entities are added: AML with mutated *NPM1* and AML with mutated *CEBPA*. Although not included as a distinct or provisional entity, examination for mutations of *FLT3* is strongly recommended in all cases of cytogenetically normal AML.

2. AML with myelodysplasia-related changes
    a. The name was changed and expanded from "AML with multilineage dysplasia" to "AML with myelodysplasia-related changes."
    b. Cases of AML are assigned to this category if (1) they have a history of MDS or MDS/MPN and have evolved to AML, (2) they have a myelodysplasia-related cytogenetic abnormality, or (3) at least 50% of cells in 2 or more myeloid lineages are dysplastic.

3. Therapy-related myeloid neoplasms. Cases are no longer subcategorized as "alkylating agent related" or "topoisomerase II-inhibitor related."

4. AML, NOS
    a. Some cases previously assigned to the subcategory of AML, NOS as acute erythroid leukemia or acute megakaryoblastic leukemia may be reclassified as AML with myelodysplasia-related changes.
    b. Cases previously categorized as AML, NOS, acute megakaryoblastic leukemia should be placed in the appropriate genetic category if they are associated with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*, or AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*. Down syndrome–related cases are excluded from this category as well.

5. Myeloid proliferations related to Down syndrome This new category incorporates transient abnormal myelopoiesis as well as MDS and AML that is Down syndrome–related. MDS and AML related to Down

syndrome are biologically identical and thus are considered together as "Myeloid leukemia associated with Down syndrome."

6. Blastic plasmacytic dendritic cell neoplasm This is a new category that includes most cases previously classified as blastic NK-cell lymphoma/leukemia or agranular $CD4^+$ $CD56^+$ hematodermic neoplasm; it is derived from a precursor of plasmacytoid dendritic cells.

Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
APL with t(15;17)(q22;q12); *PML-RARA*[*]
AML with t(9;11)(p22;q23); *MLLT3-MLL*[†]
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA
Acute myeloid leukemia with myelodysplasia-related changes[‡]
Therapy-related myeloid neoplasms[§]
Acute myeloid leukemia, not otherwise specified (NOS)
Acute myeloid leukemia with minimal differentiation
Acute myeloid leukemia without maturation
Acute myeloid leukemia with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Acute erythroid leukemia
Pure erythroid leukemia
Erythroleukemia, erythroid/myeloid
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute myelosclerosis)
Myeloid sarcoma (syn.: extramedullary myeloid tumor; granulocytic sarcoma; chloroma)
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (syn.: transient myeloproliferative disorder)
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*[‖]
Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
Mixed phenotype acute leukemia, B/myeloid, NOS
Mixed phenotype acute leukemia, T/myeloid, NOS
Provisional entity: Natural killer (NK)–cell lymphoblastic leukemia/lymphoma

or a diagnosis of AML, a marrow blast count of > 20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16) or t(16;16) and some cases of erythroleukemia.

* Other recurring translocations involving *RARA* should be reported accordingly: for example, AML with t(11;17)(q23;q12); *ZBTB16-RARA*; AML with t(11;17)(q13;q12); *NUMA1-RARA*; AML with t(5;17)(q35;q12); *NPM1-RARA*; or AML with *STAT5B-RARA* (the latter having a normal chromosome 17 on conventional cytogenetic analysis).

† Other translocations involving *MLL* should be reported accordingly: for example, AML with t(6;11)(q27;q23); *MLLT4-MLL*; AML with t(11;19)(q23;p13.3); *MLL-MLLT1*; AML with t(11;19)(q23;p13.1); *MLL-ELL*; AML with t(10;11)(p12;q23); *MLLT10-MLL*.

‡ More than 20% blood or marrow blasts *AND* any of the following: previous history of myelodysplastic syndrome (MDS), or myelodysplastic/myeloproliferative neoplasm (MDS/MPN); myelodysplasia-related cytogenetic abnormality (see below); multilineage dysplasia; *AND* absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities; cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes are:

- Complex karyotype (defined as **3** or more chromosomal abnormalities).
- Unbalanced changes: –7 or del(7q); –5 or del(5q); i(17q) or t(17p); –13 or del(13q); del(11q); del(12p) or t(12p); del(9q); idic(X)(q13).
- Balanced changes: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3;q21.1); t(2;11)(p21;q23); t(5;12)(q33;p12); t(5;7)(q33;q11.2); t(5;17)(q33;p13); t(5;10)(q33;q21); t(3;5)(q25;q34).

§ Cytotoxic agents implicated in therapy-related hematologic neoplasms: alkylating agents; ionizing radiation therapy; topoisomerase II inhibitors; others.

‖ *BCR-ABL1*–positive leukemia may present as mixed phenotype acute leukemia, but should be treated as *BCR-ABL1*–positive acute lymphoblastic leukemia.

2.2 Morphology

All patients should have a bone marrow aspirate and trephine biopsy. These may be omitted if the peripheral blast count is high and the patient is for palliative treatment only.

Blood and Marrow spreads should be stained using a May-Grunwald-Giemsa or a Wright-Giemsa Stain. The marrow slides should be particulate, and a 500 cell count performed. A 200 cell count should be performed on peripheral blood spreads. For a diagnosis of AML a blast count of 20% or more is required, except for AML with t(15;17), t(8;21), inv(16) or t(16;16) and some cases of Erythroid Leukaemia. Myeloblasts, monoblasts and megakaryoblasts are all counted as blasts. In AML with monocytic or myelomonocytic differentiation, monoblasts and promonocytes, are counted as blasts,but abnormal monocytes should not be included. Multilineage

dysplasia is defined as >= 50% dysplastic cells in two of the erythroid, megakaryocytic or granulocytic/monocytic lineages.

A trephine biopsy is essential in cases of a dry or aparticulate tap, and also if the aspirate is dilute. The trephine may reveal fibrosis and/or multilineage dysplasia where the aspirate is inadequate. Acute panmyelosis is a trephine diagnosis, requiring antibodies that identify CD34, MPO, glycophorin and megakaryocyte antigens.

Cytochemistry can be used to identify lineage involvement, although is generally superseded by immunophenotyping, detection of myeloperoxidase (MPO) in >=3% of blasts indicates myeloid differentiation. Similar staining for sudan black occurs but is less specific. A Combined Esterase stain may help determine Myeloid (Specific) and Monocytic (Non Specific) Blasts. In acute erythroleukaemia, a PAS stain may show large globules of PAS positivity. Iron stains may allow for the detection of iron stores, normal and ringed sideroblasts.

2.3 Immunophenotyping

The absence of lymphoid specific antigens cCD3 and cCD79a should be confirmed. Immunophenotyping is essential to identify AML cases that are negative for cytochemical MPO, such as FAB AML M0 (Bennett et al 1985) and AML M7 and also to identify acute leukaemias of ambiguous lineage.[1] These comprise those cases that show no evidence of lineage differentiation , acute undifferentiated leukaemia (AUL) , or those cases with a mixed phenotype. Aberrant expression of lymphoid markers such as CD7, CD19 or CD2 is a well recognised finding in AML, as is high CD33 but low CD34 expression.

Diagnosis of acute myeloid leukemia (AML)*

Precursor stage CD34, CD38, CD117, CD133, HLA-DR

Granulocytic markers CD13, CD15, CD16, CD33, CD65, cMPO

Monocytic markers NSE, CD11c, CD14, CD64, lysozyme, CD4, CD11b, CD36

Megakaryocytic markers CD41 (glycoprotein IIb/IIIa), CD61 (glycoprotein IIIa), CD42 (glycoprotein 1b)

Erythroid marker CD235a (glycophorin A)

Diagnosis of mixed phenotype acute leukemia (MPAL)†

Myeloid lineage MPO or evidence of monocytic differentiation (at least 2 of the following: NSE, CD11c, CD14, CD64, lysozyme)

B-lineage CD19 (strong) with at least one of the following: CD79a, cCD22, CD10, or CD19 (weak) with at least 2 of the following: CD79a, cCD22, CD10

T-lineage cCD3, or surface CD3

* For the diagnosis of AML, the table provides a list of selected markers rather than a mandatory marker panel.

†Requirements for assigning more than one lineage to a single blast population adopted from the WHO classification. Note that the requirement

for assigning myeloid lineage in MPAL is more stringent than for establishing a diagnosis of AML. Note also that MPAL can be diagnosed if there are separate populations of lymphoid and myeloid blasts.

Samples from Central, North west and North East sectors should be sent to:-
Central specimen Reception/Autolab
Clinical Sciences Building
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL
Urgent requests: Telephone 0161 276 6440

Samples from the Southern sector should be sent to:-
Haematology Department
Christie Hospital
Wilmslow Road
Manchester
M20 4BX
Urgent requests: Tel 0161 446 3825

2.4 Cytogenetics

All patients should have conventional cytogenetics performed. Bone marrow samples should be sent to:-

Oncology Cytogenetics
Pathology Department
Christie Hospital NHS Trust
Wilmslow Road
Withington
Manchester M20 4BX
Telephone 0161 446 3165

Seven recurrent cytogenetic abnormalities are recognized in the WHO category “AML with recurrent genetic abnormalities” and certain cytogenetic abnormalities are sufficient to establish a diagnosis of “AML with myelodysplasia related features” if the blast count is over 20%. Cytogenetics analysis may identify patients with favourable and unfavourable prognosis (Grimwade et al 2010)and the karyotype of leukaemic cells is the strongest factor in determining response to induction chemotherapy and survival (Grimwade et al 2001).

Younger adult patients are usually categorized into favourable, intermediate or adverse prognosis groups. Complex karyotype determines a consistently poor outcome.This has been redefined by MRC studies as more than 3 chromosomal abnormalities (Grimwade et al 2010), and by the WHO classification as 3 or more (Vardiman et al 2008). Additional complexity in association with t(8;21), t(16;16) or inv(16), and t(15;17) probably does not adversely affect outcome. Also excluded are cases with other recurring genetic abnormalities in the new WHO classification, such as AML with t(9;11), AML with t(6;9), as these constitute separate entities.

2.5 Molecular Diagnostics

Molecular diagnosis on marrow and blood specimens, by reverse transcriptase-PCR (RT-PCR) can be useful in certain circumstances. Recurring gene fusions such as RUNX1-RUNX1T1(previously AML1-ETO), CBFB-MYH11, MLLT3-MLL, DEK-NUP214 may still be detected even though chromosome morphology is poor, or may be requested when the chromosomal abnormality suspected on morphology is absent (Mrozek et al 2008),(Grimwade et al 2002). AML with mutations in NPM1 or CEBPA have been incorporated into the WHO classification as provisional entries (Swedlow et al 2008), and screening for these as well as FLT3 mutations may be considered in patients with cytogenetically normal AML (CN-AML). CN-AML patients with internal tandem duplications of the FLT-3 gene (FLT3-ITD) have a worse prognosis than those cases without (Kottaridis et al 2001), (Frohling et al 2002). The presence of NPM1 mutations in CN-AML has been associated with better CR rates and RFS (Dohner et al 2005), (Thiede et al 2006). The CR and RFS of patients with CN-AML and the combination of NPM1 mutation without FLT3-ITD has been likened to that of patients with t(8;21) and inv(16). A similar survival outcome has been reported in patients with mutations in CEBPA (Schlenk et al 2008), (Frohling et al 2004). A risk stratification suggested on behalf of the European LeukaemiaNet is given below.

Standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data

- Favorable
  - t(8;21)(q22;q22); *RUNX1-RUNX1T1*
  - inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
  - Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
  - Mutated *CEBPA* (normal karyotype)
- Intermediate-I*
  - Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
  - Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
  - Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
- Intermediate-II
  - t(9;11)(p22;q23); *MLLT3-MLL*
  - Cytogenetic abnormalities not classified as favorable or adverse†
- Adverse
  - inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
  - t(6;9)(p23;q34); *DEK-NUP214*
  - t(v;11)(v;q23); *MLL* rearranged
  - –5 or del(5q); –7; abnl(17p); complex karyotype‡

†For most abnormalities, adequate numbers have not been studied to draw firm conclusions regarding their prognostic significance.

‡Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions, that is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3) or t(3;3);

Molecular Screening
Trial patients
Patients in NCRN AML trials (eg AML17) will have molecular screening of presentation BM/PB carried out routinely, although clinicians will not be informed of the results, except for FLT 3 status

Non trial patients
It is recommended that patients with APL and CBF positive AML should have molecular screening of diagnostic BM/PB, including KIT mutations in CBF AML. The identification of a specific gene transcript would allow subsequent MRD monitoring. Patients who are candidates for allografting should routinely be screened for FLT 3, NPM1 and CEBPA.

A fully comprehensive Molecular Diagnostic service is not yet available in MRI, however it is for APL and CBF AML. In the interim, for screening of other mutations samples can be sent to Leeds HMDS.

2.6 Assessment of Comorbidity
Increasing age is an adverse prognostic factor (Juliusson et al 2009), even after accounting for disease specific prognostic factors, and performance status. Despite this, age in itself is not the most important factor in determining treatment related mortality, and so a careful evaluation of co-morbidities should be undertaken, so that patients suitable for intensive treatment may receive it. In addition to Medical History, Assessment of Performance Status, and Co-morbidities, other mandatory investigations for patients undergoing intensive chemotherapy include Biochemistry and urate levels, coagulation tests and urinalysis, chest film, ECG, and ECHO/MUGA, Virology for Hepatitis B C and HIV-1.

2.7 Additional investigation
Pregnancy testing and semen cryopreservation should be considered in all potentially fertile patients. HLA typing and CMV Serology should be performed in patients considered suitable for allogeneic transplantation.

Samples for HLA typing may be sent to
Transplantation Laboratory
Manchester Royal Infirmary
2nd Floor/Purple Zone
Oxford Road
Manchester
M13 9WL

3. First line therapy

3.1 Clinical trial entry
There is evidence of improved outcome for patients who have entered into clinical studies and increasingly in the management of acute leukaemia, there are further investigations which can improve diagnosis, stratification,

monitoring and access to new agents which strongly support this as a potential standard of care.

AML 17
Patients aged 16-60 should be considered for trial entry into the AML 17. Please note that patients older than the age of 60, if considered fit for a very intensive therapy can be entered into this study also.

AML16
Patients aged 60-80, should be considered for entry into the AML 16 where there is stratification for patients who are considered fit either for intensive or non-intensive therapy.

Other trials
Patients with complex karyotype who are not suitable for allogeneic transplantation are not currently catered for within the NCRN portfolio. Although these patients will frequently achieve CR with intensive chemotherapy the durability of this remission is only a matter of a few months- these patients should be considered for investigational therapy of novel agents.

3.2 Intensive induction chemotherapy

Should consist of three days of an anthracycline with cytarabine. Either in the form of DA (Daunorubicin 50mg/m2 on days 1,3 and 5 with Cytarabine 100mg/m2 12-hourly by IV push on days 1-10) or ADE (Daunorubicin 50mg/m2 on days 1,3 and 5 with Cytarabine 100mg/m2 12-hourly by IV push on days 1-10 and Etoposide 100mg/m2 by 1 hour infusion on days 1-5. No other induction regimen has been convincingly shown to be better (Lowenberg- Hematology 2003). Alternative anthracyclines have been compared including idarubicin (Vogler et al 92) and mitoxantrone (Arlin leuk 90) at comparable doses with no improvement in overall survival. High doses of cytarabine with daunorubicin have also been studied- including by the SWOG group (Weick Blood 1996) with no increase in CR but a demonstrable increase in toxicity. Priming with growth factors at induction should only be undertaken as part of a clinical trial as no studies have convincingly influenced OS (Thomas leuk 2007). Recent data is available suggesting improved CR and survival rates with higher doses of daunorubicin (Fernandez et al 2009), however the survival is comparable to MRC outcomes and the optimal dose of daunorubicin remains to be determined.

Mylotarg
Results of the AML 15 trial have indicated that the use of Mylotarg as part of induction chemotherapy does reduce the relapse risk in patients with CBF leukaemia and to a lesser extent in standard risk disease, where there is a non statisticially significant trend to benefit (Burnett et al 2010, accepted by JCO unpublished). Superiority in terms of overall survival has not yet been independently validated. This approach should therefore only continue in the context of a clinical trial.

Post remission therapy
In general most units have the greatest experience in using the MRC standard consolidation MACE (Amsacrine 100mg/m2 1 hour infusion daily days 1-5, Cytarabine 200mg/m2 daily by continuous IV infusion days 1-5, Etoposide 100mg/m2 daily by 4 hour infusion days 1-5) then MiDAC (Mitoxantrone 10mg/m2 by 1 hour IV infusion days 1-5, cytarabine 1.0g./m2 12 hourly by 2 hour infusion days 1-3). A landmark study by the CALGB has demonstrated that 4 cycles of HDAC (3g vs. 400mg vs. 100mg) leads to a survival advantage in patients with CBF leukaemia (Mayer et al 1994). The AML 15 study has yet to demonstrate significant difference between the MRC standard and varying doses of HDAC. In general standard risk patients should receive MRC consolidation for cycles 3 and 4, patients with CBF leukaemia may reasonably receive HDAC consolidation. The optimal number of cycles of therapy continues to be investigated; the current published evidence suggests this consists of 4 cycles in total. Patients with poor risk disease have a dismal outcome with conventional consolidation (Bloomfield et al 1998) and should be considered for allogeneic transplantation.

3.3 Management of older patients
The prognosis worsens with advancing years and such patients are more likely to demonstrate resistance and suffer death to initial therapy (Appelbaum et al 2006). Several studies however confirm a better quality of life and survival advantage for induction therapy compared to supportive care (Juliusson et al 2009).

Patients up to age 80
Assuming a performance status of up to 2 and no significant comorbidity or cytogenetic complexity standard induction therapy can be undertaken with an expectation of a CR rate of 50% and a treatment related mortality of up to 15% (Appelbaum et al 2006). There is limited data to properly evaluate the effect of post remission therapy. The MRC AML 11 study confirmed no advantage to a total of 4 versus 3 cycles of therapy (Goldstone et al 2001) thus shortened consolidation is standard. The overwhelming majority of these patients will relapse and should be evaluated for alternative therapy such as consolidation with reduced intensity allogeneic transplantation where appropriate such patients should be referred to Christie/MRI for assessment at the earliest opportunity.

Patients ‘over 80’ or younger with comorbidity
This group also includes those over 65 with performance status 2/3 and significant comorbidity. The MRC AML 14 (Burnett et al 2007) study has demonstrated a survival advantage for Low dose cytarabine 20mg BD SC for 10 days repeated every 28 days, when compared to hydroxycarbamide and should be considered the standard of care for such patients, although there was no benefit for patients with adverse cytogenetics such patients should be considered for investigational approaches.

Azacitidine
A phase 3 randomised trial (Fenaux et al 2009) has demonstrated a survival advantage for patient with int-2 and high risk MDS. One third of these patients

now have AML as defined by WHO and may have a survival benefit over conventional care (2 year OS 50 vs 16%) although these may be a particular group of patients with non proliferative disease, there is no data to support azacitidine in patients with greater than 30% blasts.

A new phase 3 study of azacitidine in patients with AML (greater than 30% blasts) is active at MRI contact Prof. Yin for details.

3.4 Primary refractory Disease Therapy

Failure to respond to the first cycle of induction therapy is a major predictor of a poor outcome (Schlenk et al 2003) and conventional chemotherapy then offers virtually no prospect of long term DFS. Consideration of patients age, response to initial therapy, nature of initial therapy should be considered. In general terms escalation of treatment is indicated for patients under the age of 60. There are numerous salvage regimes which have been examined one example includes FLAG IDA (Fludarabine 30mg/m2 on days 2-6, Cytarabine 2g/m2 over 4 hours on days 2-6, Idarubicin 8mg/m2 days 4-6, GCSF sc od days 1-7), published findings suggest remission can be achieved in up to 50% of such patients, and may be reasonable if there is potential for allogeneic transplantation. Patients who are not suitable for allogeneic transplantation should be considered for investigational therapy of novel agents.

4. Allogeneic Stem Cell Transplantation (SCT)

Allogeneic SCT as a post remission therapy is associated with the lowest rates of relapse. It combines chemo/radiotherapy with immunotherapy through a potent graft versus leukaemia (GVL) effect. However the benefits of allogeneic SCT have been offset by the high non-relapse mortality (NRM) of the procedure. Although single prospective trials have not shown a significant benefit in overall survival (OS) of patients undergoing allo SCT in first complete remission a meta-analysis of clinical trials that assigned allo SCT versus alternative consolidation therapies on an intent-to-treat donor versus no-donor basis show that allo SCT offers significant benefit for patients with intermediate and high risk AML (Cornelissen et al 2007). Therefore allo SCT may specially be applied to patients with a high risk of relapse and a relatively low risk of NRM. Thus for individual decision making, it is important to take into account both the disease risk, as defined by the cytogenetic and molecular genetic profile of the leukaemia and the risk associated with the transplant procedure as assessed by the co-morbidity score and other transplant-related risk indices.

<u>General recommendations for all AML patients undergoing SCT</u>

- All patients of childbearing age undergoing SCT should be offered the opportunity of preserving fertility prior to treatment, unless there are overriding clinical reasons not to do so. Contact Cheryl Fitzgerald at St Mary's Hospital tel. 0161 276 6430.

- Patients who are potential candidates for allo SCT should be discussed with and referred to the Regional Transplant Centres (Manchester Royal Infirmary and Christie Hospital) as soon as a donor is identified.

Recommendations for AML in first CR

Trial patients

- For younger patients entered in AML 17, patients designated to have a high risk score should be offered an allo SCT either from a sibling or unrelated donor.

- Older patients treated in AML 16 who have an HLA matched donor (sibling or unrelated) are eligible to receive a non myeloablative allograft (reduced intensity conditioning, RIC allograft).

Non-Trial Patients

- Good cytogenetic risk AML [t(15;17), t(8;21) and inv (16)]: allogeneic SCT is not indicated in this group of patients.

- Intermediate cytogenetic risk: Remains controversial; however most transplant physicians would currently recommend an allogeneic SCT if a matched sibling donor is available, especially for patients under 40 years of age and those who are FLT 3 mutated. The sub-group of patients who are FLT 3 wild type and NPM 1 mutated have an outcome similar to good risk patients and should not be transplanted (Schlenk et al 2008).

  The role of a MUD allograft in this cytogenetic group of patients who are FLT 3 mutated remains to be established in future trials/studies.

- Poor risk AML: this group comprises patients with poor cytogenetic risk and elderly patients (> 60 years). Allogeneic SCT should be offered to this group of patients; a search for a donor, either sibling or unrelated, should be initiated as early as possible. For elderly patients outside of AML 16, it is recommended that they are treated in well designed studies, including prospective randomised trials.

- Full intensity conditioning SCT is generally recommended for patients up to the age of 40-50 years and non-myeloablative (RIC) SCT for older patients, and those with significant co-morbidities.

Refractory and relapsed AML

Patients failing induction chemotherapy may be considered candidates for an allogeneic transplant. Allogeneic SCT offers the best prospect of a cure for patients in 2nd or higher remission.

Autograft
There is currently no role for autografting in AML, except for patients with core-binding factor positive AML and APL in 2nd CR, whose remission duration is > 1 year.

5. Relapse
In general the prognosis for patients who relapse is poor irrespective of therapy. Consideration should be given to the patients previous treatment, age, performance status, karyotype and specifically the duration of CR1. Patients who are not fit for allogeneic will generally not be suitable for intensive salvage therapy.

5.1 Salvage chemotherapy
If CR1 is less than six months
Consider for palliative care or experimental therapy. There are usually options of phase I or II trials, for such patients.

If CR1 is greater than six months, consideration should be given to high dose ARA-C based salvage chemotherapy eg. FLAG or FLAG-Ida followed by consolidation with stem cell transplantation. Patients who had durable remissions of greater than 1 year can reasonably receive reinduction therapy equivalent to their initial therapy eg DA/ADE, although this has never been examined prospectively in a randomised trial. Other agents including clofarabine (Kantarjian et al 2003) and mylotarg (Sievers et al 2001) have demonstrable activity in the relapse setting although further investigation is required to outline if they offer an advantage over more established salvage regimens.

Patients that achieve complete remission should receive allogeneic transplantation. The conditioning can be reduced intensity or full intensity transplant according to patients' age and performance status. An investigational approach for those with refractory disease that has demonstrated limited efficacy in multi centre studies includes- intensive chemotherapy with sequential RIC allograft (Schmid et al 2006), however such an approach requires validation and should ideally be undertaken as part of a clinical trial protocol.

5.2 Investigational therapy
Patients who have relapsed post transplant, early post chemotherapy or are not fit for transplant may be suitable for investigational therapy.

Current phase 2/3 clinical trials include
Clavis:- CP4055 (Elacytarabine)- fatty acid derivative of ara-C.
AstraZeneca:- AZ1152- Aurora Kinase inhibitor
Potential candidates should be discussed with Dr Mike Dennis at Christie.

Active trials at Christie can be located at:-
http://www.christie.nhs.uk/research/themes/dg/htu/default.aspx

6. Supportive care

Advances in supportive care have resulted in improvements in survival as evidenced by individuals with AML recruited to clinical trials.

The recommendations set out below offer guidance and an evidence base where available to allow local/unit policies to be developed. Individualised policies recognise the importance of identifying locally prevalent infectious organisms and drug resistance patterns.

6.1 Antibiotic prophylaxis.

The use of prophylactic antibiotics in induction chemotherapy and in neutropenic individuals undergoing consolidation chemotherapy remains controversial. The current BSCH guidelines (Milligan et al, 2006) conclude that empirical use is not recommended due to lack of evidence of a survival benefit (level IIb). The results of a large meta-analysis Cochrane review however do demonstrate that the use of prophylactic antibiotics when compared to placebo is effective in reducing overall mortality and infection related mortality in neutropenic patients (Gafter-Gvilli et al, 2005). This effect is most marked in individuals receiving quinolone antibiotics (Leibovici L et al, 2006). Recently published guidance by the European Leukamia Net recommends their use (Döhner et al, 2010).

Therefore a prophylactic quinolone antibiotic is appropriate for prophylactic use in neutropenic individuals with AML.

6.2 Antifungal prophylaxis

Fungal infections are a major cause of morbidity and mortality in the AML population, overall incidence rates of IFI were around 12% (mould 7.9% and yeast 4.4%). Death rates attributable to invasive mould or yeast infection were documented to be 38% and 35% respectively.

The use of anti-fungal prophylaxis has been shown to reduce the fungal infection related mortality when compared to placebo (Robenshtok et al, 2007). Prophylaxis with a drug active against Aspergillus species is to be preferred given the epidemiology of IFI in this patient group. A recent study suggests that posaconazole may be superior and warrants further investigation (Cornely et al, 2007).

For prophylaxis an agent with activity against Aspergillus/mould species should be selected, many units use itraconazole where the liquid formulation is preferred due to absorption issues. The initiation should be in parallel with induction of cytotoxic chemotherapy in order to ensure maximal effect at time of severe neutropenia and mucosal barrier breakdown. To be administered until neutrophil recovery of $>0.5x10^9$/L for 2 consecutive days.

6.3 Anti viral prophylaxis

This is not routinely required however can be considered in individuals receiving fludarabine/clofarabine containing regimens and with previous herpetic virus reactivation.

6.4 Pneumocystis carinii prophylaxis

Individuals receiving fludarabine/clofarabine containing regimens should receive prophylaxis against PCP infections with either septrin with alternatives of azithromycin or dapsone if not tolerated.

6.5 Tumour lysis syndrome

Metabolic derangements can occur with tumour breakdown following the initiation of cytotoxic therapy. The tumour lysis syndrome is most commonly seen in tumours with a high proliferative rate, relatively large tumour burden and a high sensitivity to cytotoxic agents. In AML predisposing factors include high WCC, high LDH and impaired baseline creatinine. It is most commonly witnessed within 12-72 hours of initiation of chemotherapy with symptoms including nausea, vomiting, oedema, overload, congestive cardiac failure, dysrhythmias, seizures, muscle cramps and tetany. Laboratory predictors of onset include hyperkalaemia, hyperuricaemia, hypocalcaemia and hyperphosphataemia which may progress to acute renal failure.

Recombinant urate oxidase (Rasburicase®) may be chosen in preference to allopurinol in high risk patients [elevated uric acid, WCC $>50x10^9$/L, LDH >x2 normal upper limit, aggressive cytoreduction and tumour infiltration of the kidneys] (Cairo et al 2004).

6.6 Growth factors

Use in induction regimes

The prolonged neutropenia, increased morbidity and early death rates, particularly notable in older individuals following intensive induction chemotherapy has resulted in numerous groups assessing the impact of colony stimulating factors. Various endpoints have been studied, most including survival, CR rates, reduction in period of neutropenia and length of hospital stay. The results have largely been similar with a demonstrated reduction in the period of neutropenia and a shorter duration of hospital stay but no demonstrable effect on CR rates or OS (Dombret et al 1995; Rowe et al 1995; Godwin et al 1998).

Most recently the largest body of prospective data from the MRC AML 11 and 12 trials has been reported. In a randomised controlled trial, placebo compared to the GCSF Lenograstim® commencing at day +8 following induction chemotherapy were compared. The time to neutrophil recovery was significantly quicker in the GCSF arm but there was no effect on severity or duration of infective complications and associated antibiotic use. Hospitalisation was however significantly reduced on average by 2 days and individuals proceeded to consolidation chemotherapy on average 3 days earlier. There was no overall effect on CR between the two arms; subgroup analysis however found a significantly lower CR rate in the GCSF arm for patients < 40 years (attributable to excess of induction death and resistant disease). No difference in outcome after remission or relapse rates (Wheatley et al 2009).

Support for the use of growth factors can be found in other international collaborative groups; the NCCN recommend consideration for older individuals based on the ECOG study Group results (Larson et al 2002). However the BCSH guidelines indicate routine use is not recommended (Milligan et al 2006) and ELN guidelines advocate individual use only (Dohner et al 2010).

The use of GCSF in induction chemotherapy can be recommended based on of quality of life and health economic decisions; its use is not however routine or widespread and local units should develop their own policy.

Use after consolidation chemotherapy
Two large trials evaluating the use of GCSF after consolidation chemotherapy demonstrated a decrease in the duration of neutropenia and a reduction in antibiotic therapy (Heil et al 1997; Harousseau et al 2000).

6.7 Transfusion support

General principles
It is standard practice in the UK that cellular blood products are leukodepleted. All patients in whom allogeneic transplantation could be considered should be given CMV negative products until their CMV status is known. Individuals receiving fludarabine/clofarabine chemotherapy require blood products to be irradiated.

Platelet transfusion
Three randomised studies have shown no significant difference in bleeding rates for a transfusion threshold of $10x10^9$/L compared to $20x10^9$/L (Heckman et al 2007); (Rebulla et al1997);(Zumberg et al 2002).The decision should be revised based on individual patient factors: mucosal bleeding, infection. Severe mucositis and fever when a higher threshold is appropriate. Although alloimmunization is less likely to occur with the use of leukodepleted products their presence should be investigated in the presence of a platelet refractory status and if confirmed HLA-matched platelets provided.

Red cell transfusion
There is no supportive evidence however 8g/dl is generally accepted as the transfusion trigger.

6.8. Neutropenic sepsis
Recognition and prompt treatment with broad spectrum antibiotics is essential. Each unit should have a policy document developed with the microbiology department.

6.9. Antifungal therapy
The following recommendations for the treatment of suspected and confirmed invasive fungal infection are based on the Guidelines form the First European Conference on Infections in Leukaemia (Herbrecht et al 2007).

Invasive candidiasis

The shift in epidemiology towards infection with non-albicans Candida such as C.glabrata and C.krusei result in infections with reduced susceptibility or resistance to azole drugs. C.glabrata is sensitive to amphoteracin and the echinocandins. C.krusei is sensitive to amphoteracin, the echinocandins and voriconazole. For invasive candida infections, Ambisome (3mg/kg) or Caspofungin is suggested until species identification and sensitivity data are available.

Invasive aspergillosis
Voriconazole and lipid formulation amphotericin are the recommended agents for use based on data from clinical studies.

6.10. Dietary advice.
Individuals receiving chemotherapy are at risk from infection from bacteria and fungus in food products. Patient advice information leaflets are available through Leukaemia Research; Dietary advice for patients with neutropenia.
Contact details; Leukaemia Research; info@lrf.org.uk,
Tel; 020 7405 0101

7. Management of special situations

7.1. Hyperleukocytosis
The condition is generally defined as a WBC >$100x10^9$/L. It is associated with higher rates of mortality in induction (Powles et al 2003). Leukostasis symptoms including retinal, cerebral or pulmonary haemorrhage require immediate treatment with leukapheresis and chemotherapy. Transfusion of packed red cells can lead to increased blood viscosity and should be avoided until wcc is less than 100 (Döhner et al 2010).

7.2. Central nervous system involvement
Leptomeningeal involvement is uncommonly observed in AML (<3%) and therefore lumbar puncture is not required as part of the routine diagnostic work-up. It should however be performed in certain clinical scenarios where there is concern. In individuals presenting with abnormal focal neurology, headache or confusion a CT/MRI scan should be performed initially to exclude an intracerebral lesion or intracranial haemorrhage with mass effect. If there is no mass effect then lumbar puncture and sampling of the CSF should be performed (microscopy, protein, glucose, cytospin). If the LP demonstrates lemtomeningeal involvement then intrathecal chemotherapy should be administered in conjunction with systemic treatment.

Drugs: CYTARABINE- 50mg IT

Regime: Initially three times weekly until blast cells are no longer detected on cytospin and then weekly for 4-6 weeks (Milligan et al 2006).

It is also reasonable to consider a consolidation regime containing HDAC which will cross the blood brain barrier.

If the initial CT scan identifies a mass lesion biopsy or needle aspiration should be considered. If a leukamic deposit is confirmed cranial radiation may be required if systemic and intrathecal chemotherapy is ineffective.
Combination chemo-radiotherapy should be avoided due to the high risk of neurotoxicity.

7.3 Management of extramedullary disease/granulocytic sarcoma.
Extramedullary disease in AML ranges from skin and gum infiltrates most frequently seen in AML of monocytic/monoblastic derivation to the rare tumorous masses (also known as granulocytic sarcomas or chloromas). The commonest sites for extramedullary myeloid tumours include skin, lymph nodes, spine, small intestine, orbit, bone, breast, cervix and nasal sinuses, but many other sites have been described. Patients presenting de novo with extramedullary leukaemia without evidence of marrow disease have in the past been managed with surgical excision or local radiotherapy as primary treatment, but almost all these patients have gone on to develop marrow disease. It is therefore recommended that patients presenting in this fashion should also receive systemic antileukaemic chemotherapy at diagnosis. Surgical or radiotherapeutic approaches may be reserved for those patients whose extramedullary tumours do not completely resolve with initial treatment.

7.4. Pregnancy

AML in pregnancy should be managed jointly between the haematologist and the obstetrician with full involvement of the mother. Chemotherapy in the first trimester is associated with a high risk of fetal malformation and should be avoided if possible. The opportunity to terminate the pregnancy should be discussed with the mother. If termination is refused and the mother's life is at risk, chemotherapy should be started. Chemotherapy in the second and third trimesters is associated with an increased risk of abortion and premature delivery as well as small for dates babies. Consideration should be given for early induced labour between cycles of chemotherapy.

8. Minimal residual disease

8.1 Core-binding factor (CBF) AML [t(8;21) and inv (16)]
There is now considerable evidence from the AML 15 Trial that MRD monitoring by RQ-PCR in CBF positive AML can identify patients at high risk of relapse. Post induction log reduction of leukaemia load is an independent risk factor for outcome: patients with log reduction of > 2-3 have a significantly better DFS and OS compared to those with < 2 log reduction. Furthermore frequent sequential monitoring of MRD after completion of chemotherapy and during remission in the first 2 to 3 years can detect molecular relapse ≥ 3 months before haematological relapse in the majority of patients. Thus MRD monitoring can potentially allow risk stratification and risk directed therapy and in cases of molecular relapse, pre-emptive therapy, for example, allografting. However, unlike in APL, the value of MRD monitoring in improving outcome in CBF AML remains to be established, and evidence of its benefit is currently largely anecdotal.

A diagnostic and interpretative service is provided by the Molecular Diagnostics Laboratory in the Manchester Royal Infirmary. We would recommend that MRD monitoring should be an integral part of the management of CBF AML. To obtain maximum information, patients should have MRD assessed after induction and after each course of consolidation therapy and during remission at 3 monthly intervals for at least 2 years post chemotherapy. Ideally paired BM and PB samples should be tested, where a BM sample is unavailable PB should be tested 2-3 monthly for MRD .

- BM and PB samples for MRD monitoring in CBF AML should be sent to the Molecular Diagnostics Laboratory, Manchester Royal Infirmary, and for discussion of problem patients, please contact Professor J A L Yin in MRI.

8.2 Acute promyelocytic leukaemia (APL)
The aim of treatment in APL is to achieve molecular negativity by RQ-PCR. Persistence or recurrence of molecular disease is invariably associated with haematological relapse. There is now strong evidence that intervention at the point of molecular persistence or recurrence is clinically useful as pre-emptive treatment with Arsenic trioxide can result in molecular negativity and prevent reinduction mortality

- In patients treated in AML 17, molecular monitoring is being carried out centrally in Guy's Hospital, London. For non-trial patients (e.g. using Spanish Protocol), we recommend a similar monitoring protocol i.e. MRD assessment in bone marrow after course 2 and subsequent consolidation courses and at 3 monthly intervals during remission for 3 years.

For non-trial patients, bone marrow samples for MRD monitoring can be sent to the Molecular Diagnostics Centre, Manchester Royal Infirmary.

9. APML
In general the diagnosis is suggested by the presence of the characteristic morphology and there is consensus that the diagnosis should be confirmed at the genetic level. However this should not delay the initiation of supportive measures or differentiation therapy which should be initiated immediately on the day of presentation without delay.

Standard Therapy
For patients who decline trial entry the standard therapy is for ATRA and anthracycline based therapy. The standard defined from AML 15 is the Spanish therapy- with superior survival compared to the MRC approach, in part due to de-escalation of chemotherapy with a reduction in treatment related mortality. Such an approach leads to a 95% complete remission rate (Sanz et al 2004) with primary resistance being an anecdotal occurence.

Comparative trials for the optimal anthracycline have not be done while there appears to be no advantage to adding cytarabine to induction therapy (Burnett blood 2007)

Course 1
Idarubicin (12mg/m2 , days 2, 4, 6, 8)and Atra(45mg/m2/day daily until CR)

Course 2
Idarubicin (7mg/m2, daily- days 1-4) and Atra (45mg/m2/day 15 days)

Course 3
Mitoxantrone (10mg/m2, daily- days 1-5) and Atra (45mg/m2/day 15 days)

Course 4
Idarubicin (12mg/m2 1 dose) and Atra (45mg/m2/day 15 days)

Consolidation therapy
Historical comparison suggests that Atra contributes to the reduction in relapse risk observed in the GIMEMA (Lococo et al 2004) and PETHEMA (Sanz et al 2004) group studies. The role of Cytarabine remains controversial and unresolved with numerous studies suggesting a reduction in relapse risk but improved survival has yet to be unequivocally demonstrated. There is no role for stem cell transplantation in first line therapy for patients with APML.

Maintenance therapy
Some patients do benefit from maintenance therapy although this is not being investigated in the current NCRN study. Patients at high risk of relapse (eg presenting wcc >10, those slow to achieve MRD negativity) can be considered for up to 2 years of Methotrexate, 6-Mercaptopurine and Atra therapy based therapy from previous studies (Tallman et al 1997, Fenaux et al 1999) which have confirmed additional efficacy.

APML Relapse
Repeated molecular relapse should be treated with **Arsenic Trioxide** (**As_2O_3=ATO**), 0.30 mg/kg IV over 2 hours daily for 5 days (days 1-5) in week 1 ,and thereafter 0.25mg/kg IV over 2 hours twice a week for an additional seven weeks. Consolidation of this remission may be in the form of further Arsenic, autologous or allogeneic transplantation. Approximately 10% of APML haematological relapses involve the CNS (Evans et al 1999) and should therefore be excluded in all relapsed patients.

Genetic variants of APML eg t (11:17)
The nature of the fusion partner of RARA is critical to Atra sensitivity. Many remain Atra sensitive and should receive standard therapy. Those which are known to be Atra resistant are usually treated as AML as sensitivity to ATO is unknown.

Minimal residual disease (MRD) monitoring by RQ-PCR- see section 8.2

Differentiation Syndrome
This is accurately defined by the presence of unexplained fever, weight gain, respiratory distress, pulmonary infiltrates, pleural and pericardial effusion, renal or cardiac failure with or without hyperleukocytosis – this necessitates immediate initiation of Dexamethasone 10mg iv intravenously 12hrly until disappearance of symptoms. If the syndrome is severe then also discontinuation of the ATRA is recommended.

The standard approach for patients at high risk of differentiation syndrome eg white cell count greater than 10 is to receive Dexamethasone 10mgs intravenously 12 hourly for the first 5 days of chemotherapy, this is based on an uncontrolled study demonstrating a low morbidity and mortality (Sanz et al 2004).

Coagulopathy
The major cause of treatment failure is induction death due to intracerebral or intra-pulmonary haemorrhage, in up to 5% of presenting patients (Tallman leuk res 2005). APTT, fibrinogen and platelet count should be checked at least twice daily during the initial phase of therapy. Correction should be managed as below until all clinical and laboratory signs of the coagulopathy have disappeared. The role of antifibrinolytic agents and heparin is at best questionable.
Coagulation: times should be kept within the normal range using FFP as replacement.
Cryoprecipitate: should be used to maintain fibrinogen levels to approximately 2 grams per litre.
Platelet count: should ideally be maintained greater than 50.

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