Guidelines for Acute Myeloid Leukemia

Taiwan AML Consortium
Evaluation and diagnosis

- History taking (including previous chemotherapy and radiation therapy) and physical examination
- Complete blood count (CBC), platelets, differential count, biochemistry profile
- Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen
- Cytochemistry of bone marrow smear or peripheral blood smear
- Immunophenotyping of leukemic cells
- Cytogenetics (karyotype +/- FISH) and genetic analyses of leukemic cells
- Check HBsAg, anti-HBcAb and anti-HCV Ab:
  1. HBsAg (+) => check HBeAg, anti-HBeAb, anti-HBc Ab, anti-HBsAb, HBV-DNA (optional);
  2. HBsAg (-) => check anti-HBs Ab, may check anti-HBcAb (optional)
- Chest X ray, EKG
- Cardiac scan if previous heart disease, prior anthracycline use, age > 60 y/o, or clinical symptoms rising concern about cardiac function
- Central venous access of choice: Port A or PICC
- CT / MRI if neurological symptoms
- Lumbar puncture (LP), if symptomatic (screening LP should be considered at first remission for patients with M4, M5 morphology with WBC count > 50 x 10^9/L at diagnosis and other subtypes of AML with WBC count > 100 x 10^9/L at diagnosis)
- HLA typing (in patients considered potential candidate for stem cell transplantation)
Diagnosis criteria

De novo AML

- Blast $\geq 20\%$ in PB or BM
  - with t(8;21), t(15;17), inv (16)/t(16;16) are considered as AML without regard to blast percentage
- Immunophenotyping: $\geq 2$ myeloid markers, typically $< 2$ lymphoid markers or myeloperoxidase (+) or nonspecific esterase/butyrate (+)

AML with myelodysplasia-related features

- Blast $\geq 20\%$ in PB or BM and
- Any of the following:
  - Previous history of myelodysplastic syndromes
  - Myelodysplastic syndrome-related cytogenetic abnormalities*
  - Multilineage dysplasia ($> 50\%$)
- Absence of prior cytotoxic therapy for an unrelated disease or recurrent genetic abnormality as described in AML.
Myelodysplastic syndrome-related cytogenetic abnormalities

• **Complex Karyotype***

• **Unbalanced Abnormalities**
  - -7/del(7q)
  - -5/del(5q)
  - i(17q)/t(17p)
  - -13/del(13q)
  - del(11q)
  - del(12p)/t(12p)
  - del(9q)
  - idic(X)(q13)

• **Balanced Abnormalities**
  - 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)

* Defined as ≥ 3 unrelated abnormalities, none of which are included in the AML with recurrent genetic abnormalities subgroup; such cases should be classified in the appropriate cytogenetic group.

** These abnormalities most commonly occur in therapy-related AML, which should be excluded before using these abnormalities are evidence for diagnosis of AML with myelodysplasia-related features.
Requirements for assigning more than one lineage to a single blast population

| Myeloid lineage | Myeloperoxidase (flow cytometry, immunohistochemistry or cytochemistry)  
|                 | **or**  
|                 | Monocytic differentiation (at least 2 of the following: non-specific esterase, CD11c, CD14, CD64, lysozyme) |
| T-lineage       | Cytoplasmic CD3 (flow cytometry with antibody to CD3 epsilon chain; immunohistochemistry using polyclonal antibody)  
|                 | **or**  
|                 | Surface CD3 (rare in mixed phenotype acute leukemia) |
| B-lineage       | Strong CD19 with at least one of the following strongly expressed: CD79a, cytoplasmic CD22, CD10  
|                 | **or**  
|                 | Weak CD19 with at least 2 of the following strongly expressed: CD79a, cytoplasmic CD22, CD10 |

- Acute erythroid leukemia: cytochemical stain may show PAS positive, CD71(+) by flow cytometry
- Acute megakaryoblastic leukemia: megakaryoblasts express CD41 +/- CD61
WHO classification 2008

AML with recurrent genetic abnormalities
- 9896/3 AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- 8971/3 AML with inv(16)(p13q22) or t(16;16)(p13;q22); CBFβ/MYH11
- 9866/3 Acute promyelocytic leukemia with t(15;17)(q22;q12); PML/RARα
- 9897/3 AML with t(9;11)(p22;q23); MLLT3-MLL
- 9865/3 AML with t(6;9)(p23;q34); DEK-NUP214
- 9869/3 AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
- 9911/3 AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
- 9861/3 AML with mutated NPM1
- 9861/3 AML with mutated CEBPA
- 9895/3 AML with myelodysplasia-related changes
- 9920/3 Therapy-related myeloid neoplasms
- 9861/3 AML not otherwise specified (NOS)
- 9872/3 Acute myeloid leukemia with minimal differentiation
- 9873/3 Acute myeloid leukemia without maturation
- 9873/3 Acute myeloid leukemia with maturation
- 9867/3 Acute myelomonocytic leukemia (AMML)
- 9891/3 Acute monoblastic and monocytic leukemia
- 9840/3 Acute erythroid leukemia
- 9910/3 Acute megakaryoblastic leukemia
- 9870/3 Acute basophilic leukemia
- 9931/3 Acute panmyelosis with myelofibrosis
- 9930/3 Myeloid sarcoma

Myeloid proliferations related to Down syndrome.
- 9898/1 Transient abnormal myelopoiesis
- 9898/3 Myeloid leukemia associated with Down syndrome.
- 9727/3 Blastic plasmacytoid dendritic cell neoplasm

Acute leukemia of ambiguous lineage
- 9801/3 Acute undifferentiated leukemia
- 9806/3 Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1
- 9807/3 Mixed phenotype acute leukemia with t(v;11q23);MLL rearranged
- 9808/3 Mixed phenotype acute leukemia, B/myeloid, NOS
- 9809/3 Mixed phenotype acute leukemia, T/myeloid, NOS
- Mixed phenotype acute leukemia, NOS-rare types
- Natural killer cell lymphoblastic leukemia/lymphoma
<table>
<thead>
<tr>
<th>Risk</th>
<th>Cytogenetics</th>
<th>Molecular abnormalities (Normal karyotype)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(15;17)</td>
<td>*Isolated <em>NPM1</em> mutation</td>
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<tr>
<td></td>
<td>t(8;21)</td>
<td>*Isolated biallelic <em>CEBPA</em> mutation</td>
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<tr>
<td></td>
<td>inv(16) or t(16;16)</td>
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<tr>
<td>Intermediate</td>
<td>Normal cytogenetics</td>
<td><em>C-KIT</em> mutation in t(8;21), inv(16)/t(16;16) (CBF leukemias)</td>
</tr>
<tr>
<td></td>
<td>* +8 alone</td>
<td></td>
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<tr>
<td></td>
<td>* t(9;11) (<em>MLLT3-MLL</em>)</td>
<td></td>
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<tr>
<td></td>
<td>* Other abnormalities not listed as favorable- and unfavorable</td>
<td></td>
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<tr>
<td>Unfavorable</td>
<td>* Complex (≥ 3 abnormalities)</td>
<td>*FLT3-ITD mutations (normal karyotype) (especially with allele burden&gt;50%)</td>
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<tr>
<td></td>
<td>* Monosomai karyotype -5, 5q, -7, 7q-</td>
<td><em>MLL</em> rearrangements other than <em>MLLT3-MLL</em></td>
</tr>
<tr>
<td></td>
<td>* Abnormalities of 11q23, excluding t(9;11)</td>
<td>*MLL-PTD mutation</td>
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<td>* inv(3), t(3;3)</td>
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<td></td>
<td>* t(6;9)</td>
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<td>* t(9;22)</td>
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<td>* t(7;11)</td>
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- Positive of core-binding factor (CBF) => do *C-KIT* mutational analysis (optional).
- Negative for recurrent genetic abnormalities (e.g. CBF and *PMR-RARα*, etc) => do *MLL* FISH analysis (optional)
Genetic lesions required to be checked at diagnosis

- **RUNX1-RUNX1T1**
- **CBFB-MYH11**
- **PML-RARα**
- **NPM1**
- **FLT3-ITD** (with allele burden)
- **MLL-PTD**
- **MLL rearrangements** \([MLLT3-MLL/t(9;11)]\)
- **CEBPA**
- **C-KIT** (in CBF leukemia)

**说明**: 以上基因变异在AML临床预后及预测早期复发有极大的价值。**卫生部**补助台大和长庚相关检测费用 (含诊断及追踪)，希望能服务其它合作医院。并依此检测结果来订定全国AML治疗规范，以提升台湾AML病人疗效及存活率。
Criteria for evaluation of treatment response

**BM examination**
- If there is a question of residual leukemia, a bone marrow aspirate/biopsy should be repeated in one week
- A bone marrow biopsy should be performed if spicules are absent from the aspiration sample
- **Complete remission (CR):**
  1. Complete hematologic remission (CHR): cellular marrow with < 5% blasts and no blasts with Auer rods; independence of transfusion; absolute neutrophils count (ANC) > 1 x 10⁹/L; platelet 100 x 10⁹/L; no evidence of extramedullary disease
  2. Cytogenetic CR: cytogenetics normal (in those with previously abnormal cytogenetics)
  3. MRD negative: target transcripts undetectable or within normal range (MLL-PTD) by RQ-PCR or < 0.1% by multi-parameter flow cytometry
  4. Major molecular response: minimal residual disease (MRD) levels 3-log reduction of transcripts compared to the pretreatment baseline by RQ-PCR or < 0.1% by multi-parameter flow cytometry
  5. CRi: morphologic CR with incomplete blood count recovery
- **Partial remission (PR):** decrease at least 50% in the percentage of blasts to 5 to 25% in BM aspirate and normalization of blood counts
- **Relapse:** reappearance of leukemic blasts in PB or more than 5% blasts in BM, not caused by regeneration after consolidation chemotherapy, or extramedullary relapse
Treatment protocol in AML (non-APL)

1. Age ≤ 65 y/o

**Induction**

**Anthracycline-based**

(1) Daunomycin 60-90 mg/m2 x 2-3 days
   Cytarabine 100-200 mg/m2 x 5-7 days

(2) Idarubicin 8-12mg/m2 x 2-3 days
   Cytarabine 100-200 mg/m2 x 5-7 days

(3) Mitoxantrone (8-12mg/m2) for 2-3 days
   Cytarabine 100 mg/m2 QD for 5-7 days

**Etoposide-based**: for patients who are not suitable for anthracyclines

   VP-16 100 mg/m² IVF x 2-3 days
   Cytarabine 100 mg/m² x 5-7 days

**FLAG or FLAG-Ida**

* May consider in age ≤ 45 y/o

   Daunomycin 60 mg/m2 or idarubicin 12mg/m2 x 3 days (day1-3)
   Cytarabine 3g/m2 q12h x 4 days (day1-4)
Post-remission therapy (Age ≤ 65 y/o)

• Risk stratification:
  – Low risk (diagnostic criteria and MRD criteria)*
    • High dose chemotherapy (Ara-C based)
    • Autologous HSCT
    • MRD monitoring
  – Intermediate
    • High dose chemotherapy (Ara-C based)
    • Allogeneic HSCT
  – High risk (diagnostic criteria and MRD criteria)*
    • High dose chemotherapy (Ara-C based)
    • Allogeneic HSCT

• Chemotherapy protocol
  – High dose cytarabine $1-3g/m^2$ q12h x 3-4 days +/- antracycline/N or etoposide for 3-6 courses
  – FLAG or FLAG-Ida
Risk stratification for post-remission therapy in Age ≤ 65 y/o

* **Low risk patients:**
  - Favorable or intermediate risk groups with **major molecular response** after 2 cycles of post-remission therapy
  - Favorable or intermediate risk groups without targets for MRD evaluation

* **High risk group:**
  - Unfavorable-risk groups at diagnosis
  - Therapy-related AML
  - Salvage therapy needed to achieve complete remission
  - Favorable or intermediate-risk groups **without** major molecular response after 2 cycles of post-remission therapy
  - **Loss** of major molecular response at any follow-up points if major molecular response previously achieved

* **Major molecular response:** MRD levels 3-log reduction by RQ-PCR or < 0.1% by flow cytometry
Age > 65 y/o and ECOG PS ≤ 2

• **Induction**
  – D(2-3 doses)A(5-7 D), I(2-3 doses)A(5-7 D), Ara-C alone, LDAC
  – Azacitidine, decitabine
  – Clinical trial

• **Post-remission**
  – Standard dose cytarabine 5-7 days +/- antracycline or etoposide
  – Intermediate dose cytarabine 1-2 g/m²
  – Low intensity cytarabine
  – High dose cytarabine 3g/m² q12h x 3 days
  – Allogeneic hematopoietic cell transplantation (reduced intensity)
  – Azacitidine, decitabine
  – **Clinical trial**
  – **Observation**
Age > 65 y/o and ECOG PS > 2, or PS ≤ 2 with significant comorbidities

• Induction
  – Ara-C alone or LDAC
  – Azacitididine, decitabine
  – Supportive treatment
  – Clinical trial

• Post-remission
  – Standard dose cytarabine 5-7 days +/- antracycline or etoposide
  – Intermediate dose cytarabine 1-2 g/m2
  – Low intensity cytarabine
  – High dose cytarabine 3g/m^2 q12h x 3 days
  – Allogeneic hematopoietic cell transplantation (reduced intensity)
  – Azacitididine, decitabine
  – Clinical trial
  – Observation
Bone marrow follow-up after induction chemotherapy

- Reappearance of blasts in peripheral blood
- After myelosuppression recovery
- Persistent pancytopenia
- Day 15 (+/-1 day) for early response evaluation (optional)

No CR or residual extramedullary disease (+)

CR and residual extramedullary disease (-)

Re-induction chemotherapy (for BM no CR on day 15+/-1 day, start re-induction chemotherapy immediately if no contraindication)

Post-remission chemotherapy
Re-induction chemotherapy

(1) I3A7 (70% dose, not I2A5)
(2) High dose cytarabine +/- antracycline or etoposide
(3) Etoposide + cytarabine +/- mitoxantrone (NEC)
(4) Fludarabine + cytarabine + G-CSF +/- idarubicin (FLAG +/- IDA)
(5) N+FLAG, V+FLAG
Evaluation and treatment of CNS leukemia

At diagnosis, neurologic symptom (+), do CT/MRI to rule out bleeding or mass effect

Mass effect (+)

Consider tissue proof

Consider cranial radiotherapy followed by intrathecal (IT) chemotherapy twice weekly until CSF clear, then once weekly for 4-6 week

Mass effect (-) screening LP*

CSF (+)

IT chemotherapy twice weekly until CSF clear, then once weekly for 4-6 week

CSF (-)

Observation

* Screening CSF study should be considered at first remission for patients with M4, M5 morphology with WBC count > 50 x 10⁹/L at diagnosis and other subtypes of AML with WBC count > 100 x 10⁹/L at diagnosis
@ IT: methotrexate 15mg alone or triple regimen with methotrexate 15mg + cytarabine 30mg + hydrocortisone 30mg
Therapy for relapsed disease

Early relapse (< 1 year)

- Clinical trial
- Chemotherapy followed by HCT
- Supportive care

Late relapse (> 1 year)

- Clinical trial
- Chemotherapy followed by HCT
- Repeat initial successful induction regimen
- Supportive care
Therapy for relapse and refractory Disease

(1) HDAC
(2) I+HDAC, N+HDAC
(3) FLAG, I+FLAG, N+FLAG, V+FLAG
(4) NEC
(5) LDAC
(6) Allogeneic HSCT
(7) Azacitidine
(8) Azacitidine + sorafenib* (for FLT3-ITD mutation)
(9) Clinical trial
(10) Supportive treatment
MRD monitoring (during and after therapy)

Genetic lesions as listed below requires monitoring by protocol

- **RUNX1-RUNX1T1**
- **CBFB-MYH11**
- **PML-RARα**
- **NPM1**
- **MLL-PTD**
- **MLL translocation** \([MLLT3-MLL/t(9;11)]\)

Sampling points for patients having MRD makers can be followed (minimal requirement):

- **At first complete remission**
- **Every two cycles of post-remission chemotherapy**
- **At the last cycle of post-remission chemotherapy**
  - After completion of all post-remission chemotherapy, follow MRD very 3 months up to one year, then every 6 month to 2-3 years
  - If MRD < 3 log reduction, further MRD follow-up is required in one month for early detection of relapse
  - Whenever there is a suspicion of AML relapse
Timeline for MRD monitoring points

If patients have no MRD targets, bone marrow follow-up after last post-remission chemotherapy can be omitted.
Guidelines for Acute Promyelocytic Leukemia

AML Consortium
Evaluation and diagnosis
• Same as other acute myeloid leukemia.

Diagnostic criteria
• M3 morphology and positive for t(15;17) by either cytogenetics or molecular analysis (PML/RARα)
Recommendation of Management

• Once a diagnosis of APL is suspected, the disease should be managed as a medical emergency.
• Treatment with ATRA should be started immediately once the diagnosis of APL is suspected on the basis of clinical findings and the peripheral blood smear (even without waiting for a bone marrow examination).
• ATRA+ATO regimen for low/intermediate risk patients
• Maintenance therapy for all high risk patients and low/intermediate risk patients who are intolerant to ATO containing regimen and receiving ATRA + chemotherapy regimen
• Steroid (10 mg dexamethasone IV bid) should be started immediately at the earliest clinical suspicion of incipient APL differentiation syndrome.
• Treatment with ATO should be restricted to cases confirmed to be PML/RARa-positive.
Induction and Consolidation Therapy

High risk (WBC > 10 x 10^9/L) (able to tolerate anthracyclines)

Induction Therapy: ATRA-based protocol

- ATRA 45 mg/m^2/day in two divided doses orally until CR plus Daunorubicin or Idarubicin or ATO +/- Ara-C: according to protocol
- Prednisolone (0.5 mg/kg/d) for 15d or Dexamethasone (2.5 mg/m^2/12 hours IV for 15 d) as clinical indicated

Consolidation therapy: ATRA-based protocol

- ATRA* plus Daunorubicin or Idarubicin or ATO +/- Ara-C: according to protocol

* ATRA administered concurrently with cycles above: ATRA 45 mg/m^2/day in 2 divided doses for 15d with each 4-wk cycle of chemotherapy

( ATRA dose is adjusted to 25 mg/m^2/d for patients < 20 years-old)
Induction and Consolidation Therapy

High risk (WBC > 10 x 10⁹/L) (unable to tolerate anthracyclines)

Induction Therapy: ATRA + Arsenic Trioxide (ATO)

- ATRA 45mg/m²/d in two divided doses orally
- ATO 0.15mg/kg/d IVF 2 hours until complete remission, or with a maximum of 60 days
- Prednisone at a dose of 0.5 mg/kg/d from D1 until the end of induction therapy as clinical indicated
- Hydroxyurea for leukocytosis as clinical indicated. (see” Special Precaution of Arsenic Trioxide”)

Consolidation:

- ATRA 45mg/m²/d 2 weeks on and 2 weeks off for a total of 7 courses
- ATO 0.15mg/kg/d IVF on Monday to Friday per weeks, 4 weeks on 4 weeks off, for a total of 4 courses
Induction and Consolidation Therapy

Low/Intermediate risk (WBC ≤ 10 x 10⁹/L)

ATRA + Arsenic Trioxide (ATO) (first priority)

Induction Therapy:

- ATRA 45mg/m²/d in two divided doses orally
- ATO 0.15mg/kg/d IVF 2 hours until complete remission, or with a maximum of 60 days
- Prednisone at a dose of 0.5 mg/kg/d from D1 until the end of induction therapy as clinical indicated
- Hydroxyurea for leukocytosis as clinical indicated. (see” Special Precaution of Arsenic Trioxide”)

Consolidation:

- ATRA 45mg/m²/d 2 weeks on and 2 weeks off for a total of 7 courses
- ATO 0.15mg/kg/d IVF on Monday to Friday per weeks, 4 weeks on 4 weeks, for a total of 4 courses

* No needs of maintenance in patients with low/intermediate risk using this protocol
Special Consideration and Response Monitoring during Induction and Consolidation Therapy

• BM aspiration with $PML/RAR\alpha$ transcripts MRD monitoring after induction and each consolidation courses till PCR(-).

• At count recovery, perform lumbar puncture for high risk patients.

- Intrathecal chemotherapy: methotrexate 15mg + cytarabine 30mg + hydrocortisone 30mg for 5 doses [IT schedule: one dose in post-induction, 2 doses (weekly) in each consolidation cycle] (optional) (Blood. 2008;111:1078-1084)
Maintenance Therapy of APL

• Maintenance therapy is **recommended in all high risk group patients and low/intermediate risk group patient receiving anthracycline-based chemotherapy protocol.** (No needs of maintenance in patients with low/intermediate risk using ATRA+ATO protocol)

  1) oral ATRA (45 mg/m$^2$/d) for 15 days every 3 months for 2 years
  2) oral mercaptopurine (50-90 mg/m$^2$/d) for 2 years
  3) oral methotrexate (5-15 mg/m$^2$/wk) for 2 years

• Doses of mercaptopurine and methotrexate are decreased by 50% if the white blood cell (WBC) count is less than 3.5 x 10$^9$/L and discontinue if it is less than 2.5 x 10$^9$/L.

• Dose adjustments of mercaptopurine and methotrexate in case of hepatotoxicity are required as clinical indicated.
Post-Consolidation Therapy and Monitoring

BM aspiration with molecular monitoring (RQ-PCR) after consolidation

RQ-PCR: negative *

Maintenance therapy per protocol

RQ-PCR monitoring up to 3 years

RQ-PCR: negative

Negative

RQ-PCR: positive

Confirm RQ-PCR in 4 weeks

First relapse

RQ-PCR: positive

Confirm RQ-PCR in 4 weeks

Negative

* RQ-PCR negative: > 4 log reduction

- Because early treatment intervention in patients with evidence of MRD affords a better outcome than treatment in full-blown relapse, every 3 months MRD monitoring of BM should be offered to all patients for up to 2-3 years after completion of consolidation therapy.
- Bone marrow generally affords greater sensitivity for detection of MRD than blood and therefore is the sample type of choice for MRD monitoring to guide therapy.
Treatment for First Relapse (I)

A. No prior exposure to ATO or late relapse (6 months) after arsenic trioxide-containing regimen

• Treat with induction course of ATRA+ATO regimen
  ➢ if 2\textsuperscript{nd} CR (morphological remission) => CNS prophylaxis and BM RQ-PCR monitoring
    – PCR negative and transplant candidate: keep consolidation course of ATRA+ATO regimen then autologous HSCT if MRD (-)
    – PCR negative but not transplant candidate: keep consolidation portion of ATRA+ATO regimen (total 6 courses)
      – PCR positive and transplant candidate: allogeneic HSCT
      – PCR positive but not transplant candidate: clinical trial
  ➢ if no remission: clinical trial or allogeneic HSCT
Treatment for First Relapse (II)

B. Early relapse (< 6 months) after ATRA or ATO only (no anthracycline)

• Treat with induction course of ATRA+ATO regimen plus Idarubicin (12 mg/m$^2$/d) IV bolus on D2, 4, 6, and 8 (3 doses of IDA for patients older than 60 years of age; 2 doses for age >70)

- if 2nd CR (morphological remission) => CNS prophylaxis and BM RQ-PCR monitoring
  - PCR negative and transplant candidate: keep consolidation course of ATRA+ATO regimen +/- anthracycline then autologous HSCT if MRD (-)
  - PCR negative but not transplant candidate: keep consolidation portion of ATRA+ATO regimen (total 6 courses) +/- anthracycline
  - PCR positive and transplant candidate: allogeneic HSCT
  - PCR positive but not transplant candidate: clinical trial

- if no remission: clinical trial or allogeneic HSCT
Supportive Care (I)

• Clinical coagulopathy and overt bleeding
  – Aggressive platelet transfusion support to maintain platelet count >50 x10^9/L during the first 10 days and, after day 10, whenever platelet count <20 x10^9/L or in the presence of hemorrhagic signs
  – Fibrinogen replacement with cryoprecipitate and fresh frozen plasma to replace clotting factors, to keep fibrinogen > 150 mg/dL
  – Prophylactic heparin use and tranexamic acid are not recommended

• Leukapheresis is not recommended in the routine management of patients with a high WBC count in APL because of the difference in leukemia biology; however, in life threatening cases with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution.
Supportive Care (II)

• APL differentiation syndrome (DS):
  – DS is diagnosed according to the presence of the following signs or symptoms: unexplained fever, increasing WBC > 10 x 10^9/L, shortness of breath, hypoxemia, pleural or pericardial effusions, renal failure, hypotension, and unexplained weight gain greater than 5 kg
  – Initiate dexamethasone at first signs or symptoms of DS (10 mg IV every 12h for 3-5 days with taper over 2wks). Consider interrupting ATRA in severe DS (≥ 4 S/S) until hypoxia resolves.

• Prophylaxis of DS
  (ATRA + Chemotherapy induction protocol):
  Prednisolone (0.5 mg/kg/d) orally for 15 days or Dexamethasone (2.5 mg/m^2/12 hours IV for 15 days
  (ATRA + ATO induction protocol):
  Prednisone at a dose of 0.5 mg/kg/d from D1 until the end of induction therapy.
Special Precaution of Arsenic Trioxide (ATO) (I)

• ATO may induce severe and prolonged myelosuppression with subsequent anemia, neutropenia, thrombocytopenia. Less frequently leukocytosis or leucopenia have been reported. Dose adjustment should be considered in case of severe side effect.

• In patients developing leukocytosis after ATO treatment -
  – Hydroxyurea: 500 mg/qid for WBC between 10 and 50 x10⁹/L
  – Hydroxyurea: 1.0 g/qid for WBC > 50 x10⁹/L
  – Hydroxyurea is discontinued when WBC count <10 x10⁹/L

• Prior to ATO therapy -
  – ECG for QTc interval evaluation, check serum Ca, Mg, K and creatinine

• During ATO therapy
  – Watch for drugs that may prolong QT interval
  – Keep K > 4mEq/dL and Mg > 1.8 mg/dL
  – Reassess patients with absolute QTc interval > 500 msec. (weekly during induction therapy and before each course of post-remission therapy)
Special Precaution of Arsenic Trioxide (ATO) (II)

- **Management of QT prolongation**
  - QTc interval was calculated using the Framingham formula. A QTc interval >450 msec for men and >460 msec for women was considered prolonged.
  - Hold ATO when QTc interval > 500msec.
  - When prolonged QTc was documented ATO and any other medication known to prolong the QTc interval should be discontinued and electrolytes should be repleted.
  - Once QTc was normalized, ATO was resumed at 0.075 mg/Kg (50%) for the first 7 days, and then if no further prolongation occurred, ATO was resumed at 0.11 mg/kg for a second week. Thereafter, if no prolongation occurred, ATO was resumed at full dose.

- **Management of Hepatotoxicity**
  - Hold ATO when AST and/or bilirubin (T) and/or alkaline phosphatase >5 times the normal upper limit (Grade 3-4)
  - When LFT < 4 times resume ATO and/or ATRA 50% dosage during first 7 days then full dosage if no previous toxicity
  - In case of reappearance of severe hepatotoxicity, discontinuation of ATO should be considered
Management of Special Situations (I)

• Older patients
  – Elderly patients in good clinical condition should be managed with a treatment approach similar to that used in younger patients slightly attenuated in dose intensity.

• Patient with severe comorbidities
  – Older and younger patients with severe comorbidities unfit for chemotherapy (especially anthracyclines) are candidates to receive ATO-based treatment schedules.

• Patients with CNS relapse
  – Induction treatment consists of weekly triple intrathecal therapy (ITT) with methotrexate, hydrocortisone, and cytarabine until complete clearance of blasts in the cerebrospinal fluid, followed by 6 to 10 more spaced out ITT treatments as consolidation. Systemic treatment should also be given.
Management of Special Situations (II)

Pregnant women

- Management of APL in pregnancy requires the involvement of the patient, hematologist, obstetrician, and neonatologist.
- Retinoids are highly teratogenic and should be avoided in the first trimester unless the patient decides to have a termination of pregnancy.
- ATRA can be used in the second and third trimesters of pregnancy.
- ATO is highly embryotoxic and is contraindicated at any stage of pregnancy.
- Although chemotherapy appears reasonably safe in the second and third trimesters, it is associated with an increased risk of abortions and premature delivery, and induction of labor between cycles of chemotherapy should be considered.

Follow-up after Completion of Consolidation Therapy

• After consolidation therapy, patient should achieve negative MRD (RQ-PCR > 4 log reduction). If patients lose negative MRD during RQ-PCR monitoring, repeat 2nd RQ-PCR test within 4 weeks to confirm molecular relapse.

• Because early treatment intervention in patients with evidence of MRD affords a better outcome than treatment in full-blown relapse, every 3 months MRD monitoring of BM cells should be offered to all patients for up to 3 years after completion of consolidation therapy.

• BM generally affords greater sensitivity for detection of MRD than blood and therefore is the sample type of choice for MRD monitoring to guide therapy.
希望參與衛福部計畫聯盟醫院的醫師配合事項

1. 申請單上務必填寫“醫師本人”手機號碼及e-mail，以利病患資料聯絡及陽性結果通知。

2. 由於資料整理需要各位參與醫院配合，以便建立一套通知檢驗結果、提醒跟催follow MRD及臨床和治療資料收集登錄的機制，如此才能分析結果，並且對衛福部補助的計畫交代成果。因此建議各醫院提供一位個案管理師當作計畫聯繫窗口（如無個管師之機構則麻煩負責主管指派一名醫師為聯絡人），方便聯絡相關事宜。

3. 由於本次衛福部計畫以提高癌登的完整性及提升AML治癒率為主，因此需要各位醫師配合提供必要的臨床資料及按時送檢MRD，如果不能配合將會影響衛福部繼續補助的意願，非常感謝大家的配合，相信對AML病人會有很大的幫助。