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백혈병 치료의 최신지견

가톨릭대학교 의과대학 부속성모병원 · 가톨릭조혈모세포 이식센타

민 우 성

Treatment of Leukemia

Min, Woo Sung, M. D.

Catholic Hematopoietic Stem Cell Transplantation Center, College of Medicine, Catholic University, Seoul, Korea

1. 진단방법의 발전 (치료전략의 다양화 필요성)

a. morphologic : FAB, conventional
b. cytochemical : conventional
c. cytogenetics : conventional -- autoanaluzer, metaphase specific
d. immunophenotyping : multiparameter flow cytometry for diagnosis, prognosis
AML M0 -- immature, no lineage specific cytochemical reactions, CD 13, 33(+)
poor outcome -- CD 13, 14, 34 coexpress
AUL(acute undifferentiated leukemia) -- previously unclassified, rare subtypes (Fig.)
e. fluorescent in situ hybridization (FISH), many various monoclonal antibodies, electromicroscopic exam, DNA gene rearrangement, MPO gene study etc.

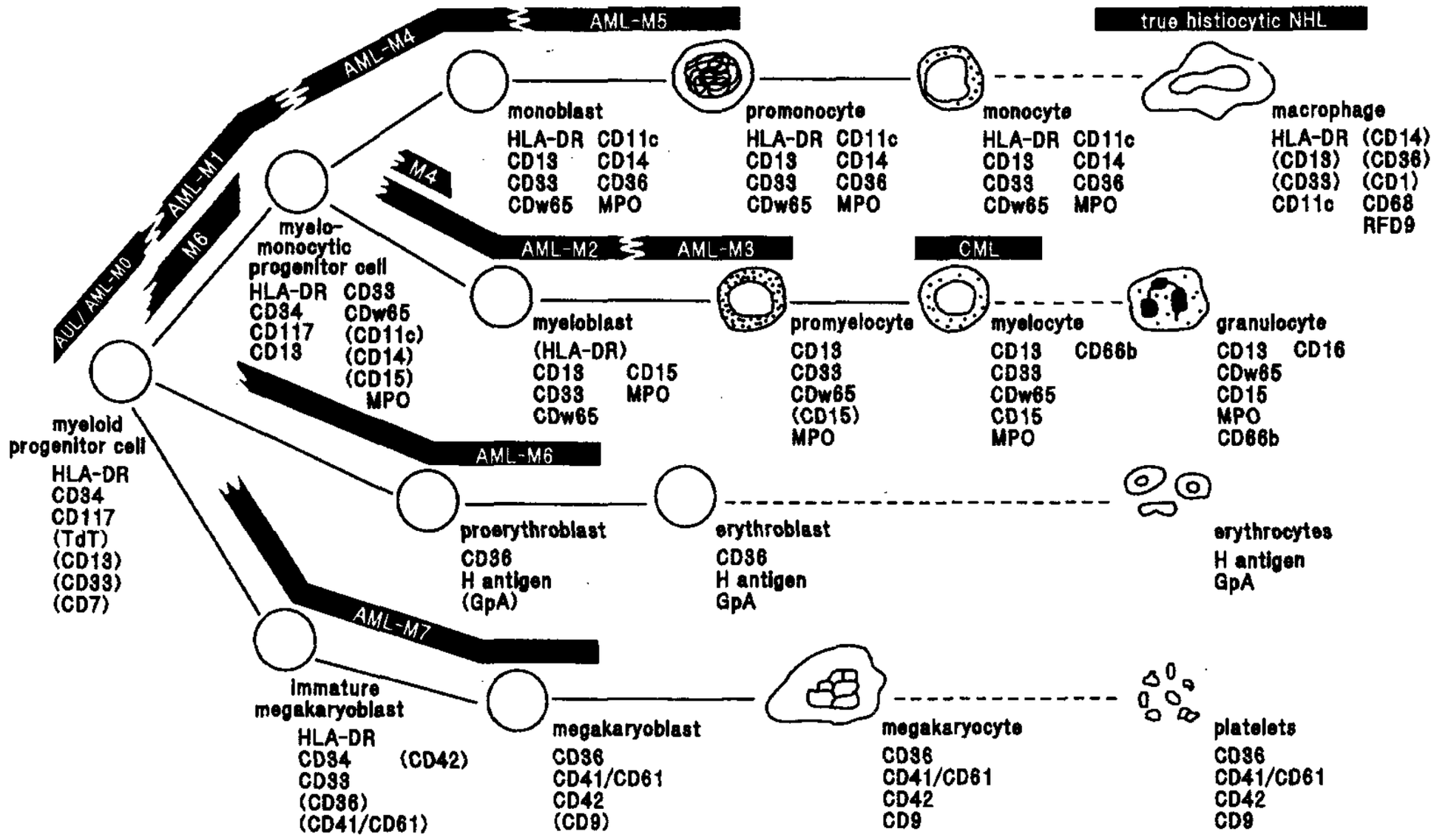
2. Clinical application of cytometry in hematologic diseases

a. Dx. of hemato-oncologic disorders : AML M0, M7, Pro-B, Pre-B, T/B-ALL, AUL, biphenotypic, billneage leukemia, etc.
b. PNH : CD55,59,66 -- GPI-linked protein defect
c. stem cell counting -- CD34+ stem cells for PBSCT
d. check DNA content
e. MDR assay
f. reticulocyte count, RMI
g. lymphocyte cross matching
h. platelet cross maching
i. lymphocyte subsetting
j. neutrophil function test

3. Drug Resistance

a. p-glycoprotein : efflux pump for chemoresistance
b. activation of intracellular detoxification system : glutathione ↑, GST ↑

Fig. Hypothetical scheme of myeloid differentiation (maturation arrest)



Hypothetical scheme of myeloid differentiation. The expression of relevant immunologic markers is indicated for each differentiation stagr ; markers in parentheses are not always expressed. The bars represent the various types of leukemias and the true histiocytic non-Hodgkin's lymphoma (NHL) and indicate where these malignancies can be located according to their maturation-arrest. It should be emphasized that most acute leukemia of the myeloid lineage have a heterogeneous phenotype, that is, they are composed of cells in multiple immature myeloid differentiation stages. To underscore this phenotypic heterogeneity, several bars fade into each other, AML = acute myelogenous leukemia, AUL = acute undifferentiated leukemia, CML = chronic myelocytic leukemia(see reference 317).

c. topoisomerase II ↓ : p-gp 억제시 더욱 감소함

d. apoptosis에 대한 내성기전(잘 일어나지 않음) :

① p53 defect or mutation, mdm2 ↑

② bcl-2 ↑, bax ↓

③ Fas-FasL 불활성화, TGF-β ↑

4. PBSC manufacturing

① steady state or rebound phase :
cyclophosphamide, 5-FU, ARA-C
cytokine stimulated or combinated

② large volume or single leukapheresis

③ CD34+ cell(positive purging) selection

④ cryopreservation

5. PBSCT

① mobilization : chemotherapy and growth factor

② rapid engraftment

③ more relapse? : purging controversy

④ post-SCT immunotherapy : for relapsing after allo-SCT

⑤ allo-PBSCT : standard stem cell source for allo-SCT in advance? mega-dose SCT

6. High dose chemoradiotherapy and auto-PBSCT

① indication : AML, ALL, CML(?)
non-Hodgkin's lymphoma, Hodgkin's lymphoma, breast cancer, neuroblastoma, small cell lung cancer, sarcoma, brain tumor etc.

② mobilized PBSCs :
CD34+ selection with Cellpro elutriator, panning, immunomagnetic beads etc.

7. Immunotherapy

① interferon-α :
CML for maintaing chronic phase, reinduction after relapsed allo-SCT, NK activity ↑, immunomodulation

② T-cell addback after allo-SCT :
T-cell seperation and CD8+ selection delayed infusion of depleted T-cell after 2-3 weeks of donor-derived stem cells → low GVHD, high GVL? less TRM

③ auto-GVHD induction :
investigational trial in clinic,
IL-2 + IFN-α/γ

8. T-cell depletion(TCD)

① purpose :
lessen the GVHD, overcome the immune barrier between unrelated or mismatched HSCT, purification of CD34+stem cells, donor engineering for modulating elderly GVHD

② method :
physical -- CCE
chemical -- lectin-based
monoclonal Ab-based -- CAMPATH+ complement, immunomagnetic microspheres, immunotoxin (ricin) binding MoAb

9. Treatment for Acute Leukmia

AML (Acute Myelogenous Leukemia; 급성골수성 백혈병)

Two phases : *induction and postremission management*

① The initial goal in treatment -
eradicate the leukemia quickly and induce CR (complete remission)

② Once CR is obtained, futher strategies to prolong survival and establisg cure

A. 관해유도화학요법(*Induction Chemotherapy*)

a. M3 아형을 제외한 모든 AML에서 가장 흔히 쓰이는 관해유도치료제 :
- cytarabine (cytosine arabinoside) and an anthracycline
- CR is achieved in 65 to 75% with de novo AML
- idarubicin may be superior to daunorubicin

* M3 : **ATRA(All-Trans-Retinoic Acid) ± Anthracycline as induction and maintenance therapeutic tools**

b. following 1st induction chemotherapy :
① bone marrow 검사 - CR or residual leukemia 여부 확인
② bone marrow on day 14 or subsequently
- 치료반응이 나쁘면 재치료하거나 chang

therapy

③ 치료반응이 없는 경우 2차 관해유도요법을 시행함

④ CR이 확인된 경우에는 가능한 조기에 bone marrow transplantion(BMT)를 고려함

⑤ 50% of patients :
resistant to the therapy administered
50% do not achieve CR :
fetal complications of bone marrow aplasia, impaired recovery of normal stem cells이 문제임

c. high-dose cytarabine-based regimens :

over 50 years old -
reduced dose, cerebellar toxicity
full cerebellar testing before each dose
further high-dose cytarabine should be witheld if evidence of cerebellar toxicity develops
-- most recently,
oral induction chemotherapy with idarubicin + VP-16(cyclic therapy)

d. synergy between cytarabine and etoposide
- improved CR duration, no change in overall survival

B. Supportive Care

① recombinant hematopoietic growth factors
- to lower the infection rate after chemotherapy
to sensitize (prime) the leukemic blasts to chemotherapy,
or to achieve both goals or to neutrophil recovery, 5 to 7 days after chemotherapy
- accelerated rate of neutrophil recovery → 감염율의 감소와 직결되지는 않음
- positive effects on CR rate and survival reported - 중증 감염율의 감소와 백혈병 세포의 증식에 변화초래

* 단, effects on disease-free survival - 없음

* thrombopoietin - shortening the duration of thrombocytopenia

② adequate and prompt blood bank support :
- platelet transfusions, maintain a platelet count above 20,000/uL should be kept at higher levels in febrile patients and during episodes of active bleeding or DIC
- poor posttransfusion platelet count increments -
administration of platelets from human leukocyte antigen(HLA)-matched donors
- intravenous immunoglobulin therapy

* red blood cell T/F - keep the hemoglobin above 85 g/L (8.5 g/dL)
* blood products leukodepleted by filtration - to avert or delay alloimmunization as well as febrile reactions
* Blood products should be irradiated to prevent graft-versus-host disease(GVHD)
* Cytomegalovirus (CMV) - negative blood products for CMV-seronegative patients : potential candidates for allogeneic BMT

③ Infectious complications :
- major cause of morbidity and of death during induction and postremission chemotherapy
- prophylactic administration of antibacterial antibiotics in the absence of fever :
controversial,
oral nystatin or clotrimazole, acyclovir prophylaxis
- latent herpes infections재활성화 예방

* fever - only half of infection pts
* early initiation of empiric broad-spectrum antibacterial and antifungal antibiotics :
- empiric amphotericin B therapy - in neutropenic patients who remain febrile without a known source for 7 days or who develop new fever while on broad-spectrum antibacterial antibiotics
- antibacterial and antifungal antibiotics should be continued until patients are no longer neutropenic, regardless of whether a specific source has been found for the fever.

* **Donor granulocyte infusion for neutropenic patients :**

ANC 500/ul >, fever with clinically documented infection, in reversible status, cytokine stimulated mobilized donor

C. Treatment Of M3 Leukemia

① daily oral ATRA during induction - improve outcome in patients with t(15;17) the cells are induced to differentiate, complications of cytotoxic therapy (e.g., DIC) are usually averted

주의 : retinoic acid syndrome -
within the first 3 weeks of therapy fever, chest pain, dyspnea, pulmonary infiltrates, progressive hypoxemia unless reversed, it can rapidly be fatal.

Tx. - aggressively early initiation of glucocorticoid therapy, oxygen, and supportive elevated leukocyte counts are at particular risk for this syndrome, addtion of chemotherapy if the leukocyte count rises above 10,000/uL

중요 : induced into CR with ATRA - 반드시 consolidation
chemotherapy 필요 - essentially all patients treated with ATRA alone ⇒ relapse

② receiving ATRA mostly remain in CR the best time for administering - still not clear

③ complete and sustained disappearance of the PML-RARa transcript by RT-PCR : high probability of maintaining diseasefree survival

D. 관해후 치료 (Postremission Therapy)

- Induction of a durable first CR is critical to long-term disease-free survival in AML
- Once relapse has occurred, AML is generally curable only by BMT.

① intensive chemotherapy and allogeneic or autologous BMT

② dose-response effect for cytarabine
the superiority of high-dose over standard - dose cytarabine

③ doses of cytarabine postremission - high (3 g/㎡ every 12 h on days 1, 3, and 5), intermediate (400 mg/㎡ for 5 days by continuous infusion), or standard (100mg/㎡ per day for 5 days by continuous infusion)

* dose-response effect for cytarabine, 60 years of age or younger
* high-dose cytarabine significantly prolonged CR and increased the fraction cured, favorable [t(8;21) and inv(16)] and normal

cytogenetics :
no significant effect on patients with other abnormal karyotypes.

④ ***allogeneic BMT*** **in first CR**, in patients under age 65 years without major organ dysfunction
(e.g., renal, pulmonary, cardiac, or hepatic damage)
+ HLA-compatible related bone marrow donor
or under age 55 years with an HLA-compatible unrelated donor, results in cure in 40 to 60 percent of patients
* toxicity is relatively high with treatment-related complications, including venoocclusive disease, GVHD, and infections

⑤ whether allogeneic BMT is superior to postremission intensive chemotherapy in first CR?

⑥ ***autologous BMT*** for postinduction therapy uses the same high-dose chemotherapy as in allogeneic BMT
- ex vivo purged marrow
- stem cells collected from the blood during the recovery phase after chemotherapy (mobilization) appear to be enriched for normal CD34+ cells, they also may be better starting material than bone marrow for subsequent selection of CD34+ subsets or other ex vivo manipulation designed to eliminate leukemic cells that may remain after mobilization

⑦ a major focus of current research -
detection of residual leukemic cells **(MRD)** in the bone marrow of CR
patients using techniques such as RT-PCR, FISH, and multiparameter flow cytometry (FACScan)

- use of **immune modulation postremission** is another experimental approach :
based on the following observations:

(1) natural killer cells are defective in patients with leukemia

(2) allogeneic transplant recipients who develop significant GVHD have a decreased risk of leukemic relapse compared with patients in whom GVHD does not develop

(3) infusion of donor leukocytes alone (without prior conditioning or GVHD prophylaxis) for relapse after allogeneic BMT ⇒ CR

→ adoptive immune response, termed graft-versus-leukemia (GVL), mediated by cytotoxic T cells, and possibly natural or lymphokine-activated killer cells,

→ may be the reason for the enhanced antileukemia effect seen in unmanipulated allografts as compared to T cell-depleted allografts

→ thus stimulation of a GVL or immunologic effect in patients with AML in remission may lead to a decreased relapse rate

* Several approaches are under investigation that attempt to **stimulate the immune system postremission** -

① low-dose (1.2×10^6 units/㎡) interleukin (IL) 2, s.c. for 10 d

→ natural killer(NK) cell expansion

→ to induce natural killer cell cytotoxicity

② the role of the multidrug resistance (MDR) gene in AML :
modulators (e.g., cyclosoporine) that can block drug efflux,
postremission chemotherapy.

E. Relapse

① once relapse occurs :
allogeneic or autologous BMT
transplanted at the first sign of relapse
- long-term disease-free survival :
30% using allogeneic BMT in first relapse or in CR2

② the most important factors predicting response at relapse :
the length of the previous CR,
whether initial CR was achieved with one or two courses of chemotherapy,
the type of postremission therapy

③ poor outcome of patients in early(<6 months) first relapse

④ longer (>12 months) first CR generally relapse with drug-sensitive disease and may achieve a second remission with the original induction regimen

⑤ long-term disease-free survival requires treatment with additional agents, not previously received, or BMT

* salvage regimens used for relapsed diease, as well as for initially refractory disease :
high-dose cytarabine with an anthracycline or mitoxantrone high-dose etoposide in conjunction with high-dose cytoxan

63명(80.8%)은 1차 관해유도요법 후,
5명(6.4%)은 2차 관해유도요법까지 시행한 이후에 성공

② 생존율에 대한 비교(추적 중앙치 12.5개월)
동종 조혈모세포 이식을 시행한 군 : 무병 생존율 85.56%
화학치료군 : 무병생존율 40.85%

③ 재발 :
전체 -- 19명(24.36%), 재발 중앙치는 300일 (35-510)
화학치료만 받은 군 - 29.27%(12/41명), 293일 (35-510)
조혈모세포 이식군 - 16.22%(6/37명), 361.5일 (60-427)
* 동종 조혈모세포이식군-13.04%(3/23명)
자가 말초혈액 조혈모세포 이식군 - 21.43% (3/14명)

2. 관해 후 이식성적
(전체성적 ; 1997년 분석)

① long-term DFS after allo-sibling-HSCT in AML : about 80%

② Autologous PBSCT : 69% DFS with 2-year follow-up

ALL(Acute Lymphoblastic Leukemia : 급성 림프구성 백혈병)

가톨릭 조혈모세포이식센타의 급성 골수성 백혈병 치료 성적

1. 관해 유도율 (IDA+BHAC를 이용한 관해 성적; 1997년 분석)

① CR(완전관해율) -- 78명중 68명(87.2%),

A. Treatment

* Clinical distinction between ALL and lymphoma :
기본적으로 골수 침범된 백분율에 의함, 따라서 유사한 적극적인 치료를 필요로 함.

(induction, consolidation, CNS prophylaxis, maintenance therapy)

a. adult ALL -
관해유도요법은 반드시 anthracycline과 vincristine, prednisone (±L-asparaginase) 포함, 이때의 CR rate는 50-85%
* 고식적 화학요법보다 더 강력한 관해유도요법의 잇점은 현재까지 보고된 바 없음.

b. CR 유도후 postremission therapy가 매우 중요 - CR기간을 증가시키기 위해

c. early CNS prophylaxis가 보다 적절 -
cranial irradiation with intrathecal chemotherapy or intrathecal and high-dose systemic methotrexate(MTX)가 효과적

d. maintenance therapy - 약 2년 지속 (소아치료와 유사)
methotrexate, 6-mercaptopurine, vincristine, and prednisone
* 단 성인에서 적절한 유지요법의 기간과 치료강도는 아직 불확실함

e. Burkitt's lymphoma in adults - 소아치료와 유사한 치료제 사용
cyclophosphamide, cytosine arabinoside, and CNS prophylaxis with MTX, 완치율은 약 60%

f. precursor T-cell and B-cell lymphoblastic lymphoma - 소아치료제이용 및 intrathecal therapy로 5년 생존율은 약 40% 재발의 주된 장소이므로 CNS 예방요법은 필수적임

B .Prognostic Factors

a. age - independent factor, older adults(>35) having a worse prognosis
기타 - delay in achiving CR, B-cell phenotype (L3 or Burkitt's), 진단시 WBC(>50,000/ul), 특이 염색체이상의 존재(t(9;22), t(8;14), t(1;19), t(4;11))
* T-cell ALL is no worse than B-cell ALL : 강력한 관해유도요법의 도입으로 인함

b. 이러한 예후인자들을 고려할 때 poor-prognosis subtypes of ALL 을 위한 독특한 치료적 접근들이 시도되어왔음. 특히 골수공여자가 있는 환자들을 위한 myeloablative therapy가 주된 관심거리임

C. Treatment of recurrent ALL and the role of BMT

a. 소아 ALL에 비해 같은 치료계획을 실행해도 CR유지기간이 짧다. 특히, 치료후 재발하거나 처음부터 관해유도에 실패한 경우는 매우 불량함. 이 경우 2차 관해에 이르더라도 기간이 매우 짧다. 유지요법이후 재발한 경우에 2차 CR이 훨씬 잘 얻어지지만 대개 모두 재발한다.

b. isolated extramedullary relapses in the CNS and testis - radiation and intrathecal therapy or radiation으로 치료하나 전신 재발을 예방하기 위해서는 재관해 유도요법을 필요로 함.

c. 성인형 재발 ALL의 경우 예후가 불량하므로 BMT를 반드시 고려해야 함
* 2차 CR상태에서 형제간 동종 골수 조혈모세포이식시행시 장기 무병생존율 : 20-30%

d. allogeneic BMT in adult with ALL in 1st CR - unclear

* 후향적, 전향적 연구에 의한 화학치료법단독과 동종 골수 조혈모세포 이식간의 3년 무병생존율(45%)은 차이가 없으며 이는 환자선택, 상대적으로 높은 이식관련 사망율, 화학 치료단독시 후기재발율의 증가 등에 기인하며 결국 이식의 필요성을 규정짓기 어려운 원인이다.
* 단, 좋지 않은 염색체유형, L3 아형, 진단시 높은 백혈구수등은 일차관해시 동종 이식을 반드시 고려하여야 한다. 즉
  t(9;22) ALL - DFS 38% with BMT,
  t(4;11) ALL etc

e. autologous BMT in 2nd remission -

* long-term leukemia-free survival in highly selected patients : 약 30%
* 일치되는 allogeneic or unrelated donors가 없는 경우 : purged or unpurged a BMT following high-dose therapy 시행함
* 단점 : treatment-related mortality는 allo BMT에 비해 의의있게 낮으나 높은 재발율이 문제 → 이유 = graft-versus-tumor effect가 없으므로

CML(Chronic Myclogenous Leukemia); 만성 골수성 백혈병

A. Traditional Treatment

① oral hydroxyurea and busulfan
② leukapheresis, plateletapheresis
③ splenectomy

B. Definitive Tx. to cure

① allogeneic hemopoietic stem cell transplantation : from sibling, familial member, unrelated donor(UBMT) -- the most possible curable disease
HLA matched or mismatched

② disadvantage of UBMT
graft failure ↑
acute & chronic GVHD ↑
prolonged convalescence following Tx.

③ BMT is the only curative therapy : survival difference is clear after 5 years of BMT > hydroxyurea/ interferon-α

C. Interferon-α :

s.c.
dose-dependent response, just prolong the duration of chronic phase not curable tool, effective when initiated within the 1st year of diagnosis as in BMT

D. Blastic Crisis

extremly poor prognosis

E. Treatment Response after IFN therapy

① HR(hematologic response)
② CR(cytogenetic response)
③ MR(molecular response) : disappearance of BCR-ABL trascript by RT-PCR

F. Autologous HSCT in CML

more recently, experimental trial
presence of CD34+ stem cells in mobilized PB

G. For relapsed after allo-BMT

① relationship of GVHD with reduced relapse

of CML

② DLI(donor T lymphocyte infusion) with or without IFN-α : **induction of graft-versus-leukemia effect, GVL**

H. GVL vs GVHD

① syngeneic BMT : no GVHD → high relapse rate

② allo-BMT : correlation between low relapse rate and high incidence of + high grade GVHD

③ autologous BMT : high relapse rate ∞ no GVHD

④ indution of GVHD by DLI after relapse of allo-BMT : remission and durable disease -free survival