Hematopoietic cell transplantation for myeloid/NK cell precursor acute leukemia in second remission

Yusuke Noguchi1, Daisuke Tomizawa1,2, Haruka Hiroki1, Satoshi Miyamoto1,3, Reiji Miyawaki1,4, Mari Tanaka-Kubota1, Tubasa Okano1, Chika Kobayashi1, Noriko Mitsuiki1, Yuki Aoki1,5, Kohsuke Imai1, Michiko Kajiwara6, Hirokazu Kanegane1, Tomohiro Morio1 & Masatoshi Takagi1

1Department of Pediatrics and Developmental Biology, Graduate School of Medicine, Tokyo Medical and Dental University, Yushima 1-5-45, Bunkyo-ku, Tokyo, Japan
2Division of Leukemia and Lymphoma, Children’s Cancer Center, National Center for Child Health and Development, Okura 2-10-1, Setagaya-ku, Tokyo, Japan
3Department of Pediatrics, Ehime Prefectural Central Hospital, Kasuga 83, Matsuyama, Ehime, Japan
4Department of Pediatrics, Matsuyama Red Cross Hospital, Bunkyo-cho, Matsuyama, Ehime, Japan
5Department of Pediatrics Oncology, National Cancer Research Center, Tsukiji 5-1-1, Chuo-ku, Tokyo, Japan
6Department of Transfusion Medicine, Graduate School of Medicine, Tokyo Medical and Dental University, Yushima 1-5-45, Bunkyo-ku, Tokyo, Japan

Correspondence
Masatoshi Takagi, Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University, 1-5-45 Bunkyo-ku, Yushima, Tokyo 113-8519, Japan.
Tel: +81-3-5803-5249;
Fax: +81-3-5803-5247;
E-mail: m.takagi.ped@tmd.ac.jp

Key Clinical Message
Myeloid/natural killer cell precursor acute leukemia (MNKPL) is a rare leukemia subtype characterized by a high incidence of extramedullary infiltration. No appropriate treatment strategy has so far been developed. Acute myelogenous leukemia-type chemotherapy combined with L-Asparaginase is an effective treatment for MNKPL. Hematopoietic cell transplantation is a second option in refractory cases.

Keywords
Hematopoietic cell transplantation, L-Asparaginase, myeloid/natural killer cell precursor acute leukemia.

Introduction
Myeloid/natural killer (NK) cell precursor acute leukemia (MNKPL) is a rare type of leukemia prevalent in Asia. MNKPL is a distinct entity in that it differs from myeloid/NK cell leukemia (MNKL) and blastic NK cell lymphoma/leukemia in terms of both morphology and immune type. MNKPL is characterized by marked extramedullary involvement, immature lymphoblastoid morphology without myeloperoxidase (MPO) reactivity, a CD7+/CD33+/CD34−/CD16+/CD15−/HLA-DR+ phenotype, myeloid chemosensitivity, and a poor prognosis. By contrast, MNKL shows no extramedullary involvement, a HLA-DR+/CD33+/CD16−/CD34−/+ phenotype, myeloid chemosensitivity, and a good prognosis. Because MNKPL is so rare, no appropriate therapeutic strategy has been established, making it hard to undertake systemic clinical trials. Therefore, accumulation of clinical observations and retrospective cohort studies will provide important information that can be used to develop future therapies.

Case Presentation
A 13-year-old Japanese boy presented to our hospital with fever, fatigue, and bilateral cervical lymphadenopathy. His...
family history did not reveal any health problems pertinent to his illness. A PET scan confirmed massive lymphadenopathy (Fig. 1A). Bone marrow aspiration revealed that 40% of the bone marrow cells comprised MPO-negative blast cells (Fig. 1B), which were CD56+/CD7+/CD33+/CD34+/HLA-DR+ (Table 1, Fig. 2A and B). A lymph node biopsy also revealed massive infiltration by blast cells+ (Fig. 2A). Immunohistochemical staining showed strong positivity for CD56, CD34, and BCL2, and moderate positivity for CD33 and MICA. Laboratory findings are shown in Table 1.

The patient was diagnosed with MNKPL, for which there is no clinically evaluated chemotherapeutic strategy. A previous report suggests that acute myelogenous leukemia (AML)-type chemotherapy may be of benefit [1], whereas other studies suggest that L-asparaginase (L-Asp) is effective against NK/T-cell-type lymphomas [2, 3]. Therefore, we used AML-type chemotherapy combined with L-Asp (10,000 U/m² 9 5 times per cycle; five cycles in total). Induction chemotherapy led to complete remission (CR). However, the leukemia relapsed (ocular involvement) after two rounds of intensification chemotherapy [4]. After local ocular irradiation and four rounds of intensification treatment, second CR was achieved and the patient was discharged. However, 1 year after cessation of chemotherapy, pancytopenia and cervical lymph node swelling re-appeared. Bone marrow

Table 1. Laboratory data on initial diagnosis.

| Peripheral blood analysis | Blood chemical analysis |
|---------------------------|-------------------------|
| WBC 1.7 × 10^9/L (Blasts, 0%) | TP 8.4 g/dL |
| RBC 4.49 × 10^12/L | BUN 4 mg/dL |
| Hb 13.7 g/dL | Cre 0.19 mg/dL |
| HCT 38.6% | LDH 408 U/L |
| Platelet 1.88 × 10^11/L | AST 51 U/L |
| Reticulocyte 14.8% | ALT 30 U/L |
| Platelet 1.88 × 10^11/L | CRP 1.62 mg/dL |
| Reticulocyte 14.8% | sIL2R 992 U/mL |

| Bone marrow examination | Cytogenetic analysis |
|-------------------------|----------------------|
| Nuclear cell count 2.6 × 10^10/L | 47,XY, +10 [7/20] |
| Megakaryocytes 15/μL | |
| Blasts 36.3% | |

Blast cells were MPO-negative/esterase-negative.

Flow cytometry analysis

| B cells | T/NK cells | Myeloid cells | Other |
|---------|------------|--------------|-------|
| CD19 2.2% | CD2 7.1% | cMPO 21.9% | CD34 98.2% |
| CD20 0.8% | CD5 0.8% | CD13 7.4% | CD38 91.5% |
| CD10 3.0% | CD3 0.6% | CD33 99.1% | HLA-DR 4.9% |
| CD7 80.2% | CD117 22.0% | |
| CD56 98.5% | CD11b 97.1% | |

MPO, myeloperoxidase.

Figure 1. (A) 18F-FDG PET/CT shows hypermetabolic lesions in multiple lymphoid organs, especially the bilateral cervical and axillar lymph nodes. FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography. (B) Wright–Giemsa staining of a bone marrow aspiration smear. Blast cells are relatively large and harbor fine azurophilic granules in the cytoplasm.
Figure 2. (A) Photomicrograph of a lymph node specimen. H-E = hematoxylin–eosin staining. Low = lower magnification, High = higher magnification. (B) Dot blot graph of flow cytometric data. The CD45 dull population was analyzed using the indicated antibody. NC = normal control IgG.
Figure 3. Clinical course of the patient. CM: cytarabine, 200 mg/m² × 7 days + mitoxantrone, 5 mg/m² × 5 days; HCEI: cytarabine, 3 g/m² q12 h × 3 days + etoposide, 100 mg/m² × 5 days + idarubicin, 10 mg/m²; HCM: cytarabine, 2 g/m² q12 h × 3 days + mitoxantrone, 5 mg/m² × 5 days; L-asparaginase, 10,000 U/m²; TIT: methotrexate, 12 mg + cytarabine, 30 mg + hydrocortisone, 25 mg; IDA-FLAG: IDA, 10 mg/m² × 5 days + fludarabine, 30 mg/m² × 5 days + cytarabine, 2 g/m² q12 h × 3 days + G-CSF, 5 µg/kg × 6 days; Capizzi: cytarabine 3 g/m² q12 h × 3 days + L-Asp, 10,000 U/m² × 5 days; LDEC: AraC, 20 mg/m² × 1 day + etoposide, 30 mg/m² × 1 day.

Table 2. Literature review of MNKPL cases.

| Case | Age | Sex | Treatment Type of HCT | Outcome | Reference |
|------|-----|-----|-----------------------|---------|-----------|
| Child cases | | | | | |
| 1 | 17 | M | AML, ALL, VP16 + AraC | Haplo BMT | Relapse after 20 months [9] |
| 2 | 12.5 | M | ALL+MIT, AraC, VP16 | | 63 months [7] |
| 3 | 8.5 | M | ALL+MIT, AraC, VP16 | | 38 months [7] |
| 4 | 1.3 | M | ALL+MIT, AraC, VP16 | | 26 months [7] |
| 5 | 3.8 | M | ALL+MIT, AraC, VP16 | | 7 months[4] |
| 6 | 5 | F | AML+L-Asp | | 40 months [10] |
| 7 | 6 | F | AML+L-Asp | | 46 months [11] |
| 8 | 1 | M | AML, ALL | | HLA mis related BMT 7 months after HCT[3] |
| 9 | 14 | F | AraC, ADR, VP16 | Sib BMT | ND [13] |
| 10 | 18 | M | ALL | Sib BMT | Relapse after 1 month[4] |
| 11 | 2 | M | ALL, AML+L-Asp | CBT | 24 months [3] |
| 12 | 0.9 | F | VCR, ADR, CPM | Auto BMT | 3 months[4] |
| 13 | 19 | M | CHOP+L-Asp, DCVP | Related BMT | 19 months[4] |
| Adult cases | | | | | |
| 1 | 63 | M | Before chemotherapy[4] | | [16] |
| 2 | 21 | M | DOAP, IDA, AraC, FLAG | | ND [8] |
| 3 | 74 | F | | ND | [17] |
| 4 | 62 | M | | ND | [17] |
| 5 | 34 | M | MIT, AraC, VP16 (after HCT) | Unrelated BMT | 24 months [18] |
| 6 | 37 | F | AraC, IDA | | 1 month[4] |
| 7 | 36 | M | MIT, AraC, VP16 | Unrelated PBSCT | Donor derived MDS at 7 months[4] |
| 8 | 34 | M | AraC, IDA | | ND [21] |
| 9 | 34 | M | CHOP, DCVP | | 17 months[4] |
| 10 | 46 | M | DCVP | | 4 months[4] |
| 11 | 54 | M | DCMP | | 30 months[4] |
| 12 | 29 | F | DCMP | | Sib BMT 19 months due to GVHD[4] |
| 13 | 48 | M | ALL | | 41 months[4] |
| 14 | 59 | M | Low dose AraC, DCVP | | 11 months[4] |

HCT, hematopoietic cell transplantation; AML, AML-type chemotherapy; ALL, ALL-type chemotherapy; AraC, cytarabine VP16, etoposide; MIT, mitoxantrone; L-Asp, L-asparaginase; ADR, adriamycin; CPM, cyclophosphamide; CHOP, CPM + ADR + vincristine (VCR) + prednisolone (PSL); DOAP, daunorubicin (DNR) + VCR + AraC + PSL; DCMP, daunorubicin (DNR) + AraC + 6-mercaptopurine + PSL; DCVP, DNR + AraC + VCR + PSL; BMT, bone marrow transplantation; Haplo BMT, haploidentical matched BMT; CBT, cord blood transplantation; PBSCT, peripheral blood stem cell transplantation; HLA, human leukocyte antigen; sib, sibling; mis, mismatch; auto, autologous.

†Dead.
aspiration revealed bone marrow relapse. Therefore, the patient received idarubicin (IDA) combined with FLAG induction therapy, followed by one cycle of FLAG, Capizzi, and LDED intensification therapy. Second CR was again achieved. The patient then underwent hematopoietic cell transplantation (HCT) with 8/8 HLA-matched unrelated bone marrow. The conditioning regimen comprised total body irradiation (TBI; 12 Gy) and melphalan (60 mg/m²/day for 3 days). Tacrolimus (0.02 mg/kg/day) and methotrexate (MTX; 15 mg/m² on Day 1 and 10 mg/m² on Days 3, 6, and 11) were used for graft versus host disease (GVHD) prophylaxis. Engraftment was achieved by Day 21. Grade I GVHD was observed. Regimen-related toxicity was moderate. The patient stayed in remission for 2 years after HCT (Fig. 3).

Discussion

Several case reports describing MNKPL have been published. It should be refrain that MNKPL is different entity to be distinguished from MNKL. MNKPL has a poor prognosis, whereas the prognosis for MNKL is much better. MNKPL is characterized by CD34 antigen-positivity and extramedullary involvement [1, 5]. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia does not mention MNKPL, but it may be categorized as AML with minimal differentiation or mixed phenotype acute leukemia, and not otherwise specified rare types (MPAL NOS rare types) [6].

MNKPL shows a better therapeutic response to AML chemotherapy regimens than to ALL regimens [1], and L-Asp as a single agent is an effective treatment for relapsed/refractory NK/T-cell lymphomas [2, 3]. Based on these observations, L-Asp has been incorporated into AML-type regimens used to treat several cases, including our own.

A literature review identified 13 pediatric (less than 20 years of age) MNKPL cases (Table 2). The age of onset was between 0.9 and 19 years of age (mean, 8.3 years), and nine of 13 cases were male (69%). Six cases survived and were disease free (observation period, 24–63 months), and seven cases received AML-type chemotherapy during the induction, consolidation, or intensification phase. On the other hand, Guan et al. reported that the ALL-type regimen was effective in three MNKPL cases when using cytarabine, mitoxantrone, etoposide, (an agent used for the treatment of AML) and L-Asp as a single agent is an effective treatment for relapsed/refractory NK/T-cell lymphomas [2, 3]. Based on these observations, L-Asp has been incorporated into AML-type regimens used to treat several cases, including our own.

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The incidence of MNKPL is low. Therefore, no systemic clinical trial to develop an appropriate therapeutic approach has been undertaken. In this case, collection of case reports is essential. In addition, international collaborations will speed up progress toward developing a standard treatment plan.

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Authorship

YN: drafted the manuscript. YN, DT, HH, SM, MariT, RM, MTK, TO, CK, NM, and YA: participated in patient care and data correction, and helped with the literature review. MK: managed HCT. KI, MK, HK, TM, and MT: supervised manuscript preparation and performed proofreading of the final manuscript.

Conflict of Interest

None declared.

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