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The Division conducts clinical, pathological, and therapeutic research on hematological diseases, including hematopoietic tumors. In the field of genomic medicine, which has been developing in recent years, research is also being conducted for clinical application. In collaboration with HGC, our laboratory conducts research on clinical sequencing, curation through artificial intelligence, automation and efficiency of clinical implementation, and clinical significance of clinical sequencing. In ATL, we have also developed novel clinical markers to elucidate the prognostic significance of HAS-Flow and predict the development of ATL by measuring PVL in HTLV-1 carriers. In the field of adult histiocytosis, we treat a large number of cases as one of the leading clinical facilities in Japan and are responsible for the development of Japanese guidelines. We are also involved in the elucidation of clonal progression in histiocytosis. We are also working to improve the clinical practice of transplantation through the analysis of HSCT data.

1 Allogeneic hematopoietic cell transplantation for patients with acute myeloid leukemia not in remission.

Flow cytometric profiles with CD7 and CADM1 in CD4+ T cells are promising indicator for prognosis of aggressive ATL

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Adult T-cell leukemia/lymphoma (ATL) is a poor prognosis hematological malignancy originating from human T-cell leukemia virus (HTLV)-1-infected CD4+ T cells. Flow cytometric plots of CADM1 and CD7 in CD4+ T cells are useful for separating HTLV-1-uninfected T cells and ATL cells. They are indicators of clonal evolution of HTLV-1 infected cells and disease progression of asymptomatic carriers or indolent ATL. However, the impacts of the plots on the clinical course or prognosis of ATL, especially in

aggressive ATL, remain unclear. We focused on the N fraction (CD4 + CADM1 + CD7-) reflecting ATL cells and analyzed the flow cytometric profiles and clinical course of 497 samples from 92 HTLV-1-infected patients that were mainly aggressive ATL. The parameters based on N fractions showed significant correlations with known indicators of ATL disease status (sIL-2R, LDH, abnormal lymphocytes, etc.) and sensitively reflected the treatment response of aggressive ATL. The parameters based on N fractions significantly stratified the prognosis of aggressive ATL at four different time points: before treatment, after one course of chemotherapy, at the best response after chemotherapy, and before allo-HCT. Even after mogamulizumab administration, which shows potent effects for peripheral blood lesions, the N fraction was still a useful indicator for prognostic estimation. In summary, this report shows that CADM1 versus CD7 plots in CD4 + T cells are useful indicators of the clinical course and prognosis of aggressive ATL. Therefore, this CADM1 and CD7 profile is suggested to be a useful prognostic indicator consistently from HTLV-1 carriers to aggressive ATL.

2 Prognosis of aggressive adult T-cell leukemia/lymphoma with central nervous system infiltration and utility of CD7 versus CADM1 flow-cytometric plots of cerebrospinal fluid

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The prognosis of adult T-cell leukemia/lymphoma (ATL) with primary central nervous system (CNS) involvement has been unclear since the advent of new therapies. Recently, we have shown that flow cytometric CD7/CADM1 analysis of CD4 + cells (HAS-Flow) is useful to detect ATL cells that are not morphologically diagnosed as ATL cells. We investigated the role of CNS involvement in ATL using cytology

and HAS-Flow by analyzing cerebrospinal fluid (CSF) from 73 aggressive ATL cases. Based on the findings in CSF, the study subjects were classified into CNS + (cytologically malignant, n = 18), CNS- (cytologically non-malignant and ATL cell population negative in HAS-Flow, n = 44), and CNS-Micro (cytologically non-malignant and ATL cell population positive in HAS-Flow, n = 11) groups. As expected, the CNS + group had a shorter overall survival than the CNS- groups ($P < 0.001$). However, the CNS-Micro group showed no adverse impact on overall survival compared to the CNS- group ($P = 0.506$), even without additional CNS-targeted treatments. HAS-Flow also demonstrated clinical utility in the diagnosis of CSF lesions in ATL patients with cerebral white matter lesions and in the detection of ATL cells on post-treatment CSF examination in patients with CNS involvement. Our study demonstrates that ATL with CNS involvement have a poor prognosis and that CSF HAS-Flow is useful to assist in the diagnosis of suspected CNS involvement and to detect ATL cells with high sensitivity after treatment.

3 Mathematical Model for Long-Term Kinetics of Proviral Load in HTLV-1 Carriers: Prospective Risk Estimation for the Development of Adult T-cell Leukemia/lymphoma

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In HTLV-1 asymptomatic carriers (ACs), high proviral load (PVL) is a risk for developing ATL. PVL values has been assumed to be unchanged for each ACs over at least 10 years of observation, and the same

threshold for risk of developing ATL has been applied regardless of age. To determine the dynamics of PVL for each ACs, we applied mathematical analysis for the population data including 1371 samples from 252 ACs (median of 4 samples per case, range:2-15) at wide range of ages (16-79). This study was conducted with cooperation of JSPFAD. Analysis of PVL from the whole samples showed clear trend to increase with age, and trajectory analysis using linear function model for PVL logarithm data revealed six groups based on the intercept and slope of the linear model. Of these, one group (12%) with a high initial value and a high rate of increase was designated as the high risk group, followed by two groups as the high-intermediate (21%) and low-intermediate risk groups (22%) respectively, and three groups with low initial values were designated as the low risk group, of which two groups showed no significant increase along with age. To examine clinical significance of this model, we applied this model to 15 patients who developed from ACs to ATL (not included the model generation), and showed that 12 cases were classified in the high risk, 2 in the high-intermediate risk, and 1 in the low-intermediate risk group, while none were included in the low risk group. This model is expected to be used to prospectively estimate the risk of developing ATL in ACs based on age and PVL value.

4 Multi-hit somatic mosaicism of TP53 pathogenic variants in a patient mimicking Li-Fraumeni syndrome

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We present a case of a 38-year-old female initially suspected of having Li-Fraumeni syndrome based on her history of early-onset anaplastic oligodendroglioma and subsequent therapy-related myelodysplastic syndrome. Genetic analysis revealed two pathogenic

TP53 variants: c.818G>A p.(Arg273His) and c.659A>C p.(Tyr220Ser). Further investigation using multiple tissue samples demonstrated varying variant allele frequencies, confirming somatic mosaicism rather than germline mutations. This case represents the first report of biallelic TP53 mosaicism, highlighting the challenges in distinguishing between germline and somatic mosaic variants and the implications for cancer risk assessment, surveillance, and genetic counseling (manuscript in preparation).

5 Collaborative Research with Fujitsu Ltd.: Development of AI-based Pathogenicity Prediction System for Gene Fusion in Cancer Research Project: Pathogenicity Prediction of Gene Fusion in Structural Variations: A Knowledge Graph-Infused Explainable Artificial Intelligence (XAI) Framework

Principal Investigators:

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From Fujitsu Research: Masaru Fuji

Project Members:

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From Fujitsu Research:

Shin-Ichiro Tago, Katsuhiko Murakami, Sho Takishita, Hiroaki Morikawa, Rikuhiko Kojima

Project Summary:

This collaborative research between The Institute of Medical Science, The University of Tokyo (IMSUT) and Fujitsu Ltd. aims to develop an innovative AI system for predicting pathogenicity in cancer-related structural variants. By combining IMSUT's expertise in cancer genomics with Fujitsu's advanced AI technology, the project successfully developed a highly accurate prediction system that can also explain its decision-making process, marking a significant step forward in genomic medicine (PMID: 38791993).

6 Genetic Debulking Before Allogeneic Stem Cell Transplantation for Myelodysplastic Syndrome Using the Molecular International Prognostic Scoring System

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Allogeneic hematopoietic stem cell transplantation (aHSCT) is the only curative therapy for patients with myelodysplastic syndrome (MDS). The Revised International Prognostic Scoring System (IPSS-R) is most frequently used for risk stratification of MDS. However, it remains unclear whether bridging therapy before aHSCT improves disease outcomes. Recently, the Molecular International Prognostic Scoring System (IPSS-M), which considers the genetic profile of MDS, has been developed. Using clinical and genetic data, we are currently analyzing the impact of lowering the IPSS-M score before aHSCT.

7 A prospective analytical study of minimal residual disease after allogeneic hematopoietic stem cell transplantation using circulating tumor DNA in acute myeloid leukemia: KSGCT1702

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【Background】

Post-allogeneic relapse of AML/MDS is an important clinical issue, and there is a need to develop a non-invasive method to detect relapse at an early stage

【Purpose】

To evaluate the usefulness of the minimal residual disease assay, which measures driver mutations identified by comprehensive genetic analysis in post-transplant AML/MDS patients by VAF of circulating tumor DNA in post-transplant patients' serum, in transplant patients in the Kanto Hematopoietic Stem Cell Group.

【Subjects】

Patients diagnosed as AML/MDS cases according to WHO Classification 2008, aged 20 to 65 years, who may undergo allogeneic hematopoietic stem cell transplantation with myeloablative pretreatment at KSGCT participating centers, and whose written consent has been obtained from the patient

Enrollment period: June 2018 - June 2021

Number of patients: 70 patients

Primary endpoint: comparison of one-year cumulative relapse rate by the presence or absence of ctDNA persistence after transplantation

【Method】

Target cases will be enrolled and next-generation sequencing will be performed on tumor and control (oral mucosa) specimens. Driver gene mutations will be identified and a Droplet Digital PCR (ddPCR) assay will be designed. Cell free DNA will be extracted from serum samples before and after bone marrow transplantation, and driver gene mutations will be quantitatively measured using ddPCR.

【Progress】

A total of 70 cases from 12 centers were included in this study. Of these, 12 cases were lost to follow-up

before allogeneic haematopoietic stem cell transplantation and 58 cases underwent allogeneic haematopoietic stem cell transplantation. Fifteen cases relapsed within 1 year of transplantation and 10 cases died within 1 year of transplantation, including 1 case of death before transplantation and 4 cases of death due to relapse.

Next-generation sequencing (NGS) was performed in 58 patients to identify driver gene mutations. This identified driver gene mutations in 51 cases that could be targeted for MRD measurement.

The median age of the 51 patients was 53 years (range: 25-65 years) and 60.8% (31 cases) were male. The diagnosis was acute myeloid leukaemia (AML) in 88.2% (45 cases) and myelodysplastic syndrome (MDS) in 11.8% (6 cases). In addition, umbilical cord blood was used as the source of transplantation in 54.9% (28 cases) and the disease status at the time of transplantation was complete remission (CR) in 54.9% (28 cases).

In addition, 74.5% (38 cases) had chromosomal abnormalities at diagnosis and 33.3% (17 cases) had an unfavourable prognosis according to the European LeukemiaNet (ELN) 2022 risk classification.

In the 51 cases in which we identified drivers for MRD measurement, we identified 60 variants for Point mutation and insertion deletion and 10 variants for Fusion as driver gene mutations.

Point mutation and insertion deletion were more common in NPM1 and NRAS, while fusion was more common in KMT2A related and CBFβ-MYH11.

MRD was measured in cell free DNA at 30, 60, and 90 days after transplantation for driver gene mutations in 45 patients. 22, 12, and 13 patients were MRD positive at 30, 60, and 90 days, respectively. MRD-positive cases at 30, 60, and 90 days post-transplant tended to have higher cumulative recurrence rates. Statistical analysis, including survival analysis, and preparation for submission for publication are currently underway.

8 A prospective analytical study of minimal residual disease after allogeneic hematopoietic stem cell transplantation using circulating tumor DNA in acute lymphoid leukemia: KSGCT1901

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【Background】

Post-allogeneic relapse of ALL is an important clinical issue, and there is a need to develop a non-invasive method to detect relapse at an early stage

【Purpose】

To evaluate the usefulness of the minimal residual disease assay, which measures driver mutations iden-

tified by comprehensive genetic analysis in post-transplant ALL patients by VAF of circulating tumor DNA in post-transplant patients' serum, in transplant patients in the Kanto Hematopoietic Stem Cell Group.

【Subjects】

Patients 16 years of age or older, acute lymphoblastic leukemia according to WHO classification 2016, any history of chemotherapy at the time of transplantation, specimens with tumor volume of at least 20% available, potential for allogeneic transplantation, and written consent obtained from the patient.

Enrollment: July 2020 - March 2023

Primary endpoint:

Comparison of one-year cumulative recurrence rate by the presence or absence of residual ctDNA after transplantation

Target cases: 55 cases

【Method】

Target cases will be enrolled and next-generation sequencing will be performed on tumor and control (oral mucosa) specimens. Driver gene mutations will be identified and a Droplet Digital PCR (ddPCR) assay will be designed. Cell free DNA will be extracted from serum samples before and after bone marrow transplantation, and driver gene mutations will be quantitatively measured using ddPCR.

【Progress】

There were 54 cases enrolled, 5 cases of pre-transplant dropout, and 43 cases of transplantation performed. NGS of tumor samples was performed in 40 cases and driver gene mutations were identified in 24 cases. A Droplet Digital PCR assay is being designed for each case.

9 Common progenitor origin for Rosai–Dorfman disease and clear cell sarcoma

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Histiocytic neoplasms (HNs) in adults have been reported to be associated with a high prevalence of coexisting hematological and solid malignancies. While part of coexisting HNs and hematological malignancies share identical HNs and hematological malignancies share identical genetic alterations, the genetic association between HNs and solid malignancies has not been scarcely reported. We report a case of Rosai–Dorfman disease (RDD) complicated by coexisting clear cell sarcoma (CCS). RDD is a rare HN. CCS is an ultrarare soft tissue sarcoma with a poor prognosis. Mutation analysis with whole-exome sequencing revealed six shared somatic alterations including *NRAS* p.G12S and *TP53* c.559 + 1G>A in both the RDD and CCS tissue. This is the first evidence of a clonal relationship between RDD hematological and solid malignancies using mutational analysis. We hypothesize that neural crest cells, which originate in CCS, are likely the common cells of origin for RDD and CCS. This case helps to unravel the underlying clinicopathological mechanisms of increased association of solid malignancies in histiocytic neoplasms.

10 Clinical and prognostic features of Langerhans cell histiocytosis in adults

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Langerhans cell histiocytosis (LCH) is a rare disease characterized by clonal expansion of CD1a + CD207 + myeloid dendritic cells. The features of LCH are mainly described in children and remain poorly defined in adults; therefore, we conducted a nationwide survey to collect clinical data from 148 adult patients with LCH. The median age at diagnosis was 46.5 (range: 20–87) years with male predominance (60.8%). Among the 86 patients with detailed treatment information, 40 (46.5%) had single system LCH, whereas 46 (53.5%) had multisystem LCH. Moreover, 19 patients (22.1%) had an additional malignancy. *BRAF* V600E in plasma cell-free DNA was associated with a low overall survival (OS) rate and the risk of the pituitary gland and central nervous system involvement. At a median follow-up of 55 months from diagnosis, six patients (7.0%) had died, and the four patients with LCH-related death did not respond to initial chemotherapy. The OS probability at 5 years post-diagnosis was 90.6% (95% confidence interval: 79.8–95.8). Multivariate analysis showed that patients aged ≥ 60 years at diagnosis had a relatively poor prognosis. The probability of event-free survival at 5 years was 52.1% (95% confidence interval: 36.6–65.5), with 57 patients requiring chemotherapy. In this study, we first revealed the high rate of relapse after chemotherapy and mortality of poor responders in adults as well as children. Therefore, prospective therapeutic studies of adults with LCH using targeted therapies are needed to improve outcomes in adults with LCH.

11 Yanada M1,2, Yamasaki S3, Kondo T4, Kawata T5, Harada K6, Uchida N7, Doki N8, Yoshihara S9, Katayama Y10, Eto T11, Tanaka M12, Takeda S13, Kawakita T14, Nishida T15, Ota S16, Serizawa K17, Onizuka M6, Kanda Y18, Fukuda T19, Atsuta Y20,21, Konuma T22.

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Allogeneic hematopoietic cell transplantation (HCT) is the last option for long-term survival for patients with chemotherapy-refractory acute myeloid leukemia (AML). By using the Japanese nationwide registry data, we analyzed 6927 adults with AML having undergone first allogeneic HCT while not in complete remission (CR) between 2001 and 2020. The 5-year overall survival (OS), relapse, and non-relapse mortality (NRM) rates were 23%, 53%, and 27%, respectively. Multivariate analysis identified several factors predictive of OS mainly through their effects on relapse (cytogenetics, percentage of blasts in the peripheral blood, and transplantation year) and NRM (age, sex, and performance status). As regards disease status, relapsed disease was associated with a higher

risk of overall mortality than primary induction failure (PIF). The shorter duration of the first CR increased the risks of relapse and overall mortality for the relapsed group, and the longer time from diagnosis to transplantation did so for the PIF group. Our experience compiled over the past two decades

demonstrated that >20% of patients still enjoy long-term survival with allogeneic HCT performed during non-CR and identified those less likely to benefit from allogeneic HCT. Future efforts are needed to reduce the risk of posttransplant relapse in these patients.

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