（報告様式４）

【16ck0106189h0002】

平成 29 年　5 月　31 日

平 28 年 度　委 託 研 究 開 発 成 果 報 告 書

I.　基本情報

事　業　名：（日本語）革新的がん医療実用化研究事業
（英　語）Practical Research for Innovative Cancer Control

研究開発課題名：（日本語）チロシンキナーゼ阻害薬による慢性骨髄性白血病の治癒を目指した研究
（英　語）Studies to optimize the use of tyrosine kinase inhibitors as a curative tool in chronic myeloid leukemia

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実　施　期　間：　平成　28 年　　4 月　　1 日　～　平成　30 年　　3 月　　31 日

分担研究開発課題名：（日本語）チロシンキナーゼ阻害薬による慢性骨髄白血病の治癒を目指した研究
慢性骨髄性白血病の長期無再発をもたらす免疫学的機序の検討
（英　語）Successful treatment free remission in chronic myeloid Leukemia under the immunological mechanism induced by tyrosine kinase inhibitor

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分担研究開発課題名：（日本語）統計およびデータ解析
（英　語）Statistics and data analysis

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分担研究　　（日本語）CML 細胞の遺伝子変異解析
開発課題名：　（英　語）Mutation analysis of CML cells

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分担研究　　（日本語）遺伝子変異の検証と統合的解析
開発課題名：　（英　語）Validation of somatic gene mutations detected by whole exome sequencing and integrated analysis of CML pathogenesis and treatment outcome

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分担研究　　（日本語）臨床研究データの収集と管理
開発課題名：　（英　語）Data management of the clinical study

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分担研究　　（日本語）CML 細胞に対するゲノムワイドな遺伝子解析
開発課題名：　（英　語）Genome-wide　analysis of CML cells

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分担研究　　（日本語）施設審査・監査 検体保存
開発課題名：　（英　語）Site visit, auditing, Storing samples
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分担研究　　（日本語）CML 幹細胞の解析
開発課題名：　（英　語）Analyses of CML stem cell properties

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分担研究　　（日本語）次世代シークエインサーを用いたRNAseq解析
開発課題名：　（英　語）Comprehensive analysis of BCR-ABL mutant by next-generation sequencing

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II. 成果の概要（総括研究報告）

1.臨床試験の進捗状況

1）STIM213試験：2年間以上分子遺伝学的完全寛解（CMR; MR4.5以上の治療効果）を維持した慢性期CML症例に対するイマチニブの中止試験

STIM213試験ではすでに目標症例の登録を終了しており、全例でイマチニブが中止されている。主要評価項目である12ヶ月の無治療分子遺伝学的寛解（Treatment Free Remission: TFR）の維持率は約69%であった。イマチニブ中止後もTFRを維持している症例において継続的に再発の有無を観察中である。観察中にTFRを喪失した症例では速やかにイマチニブを再開し、ほとんどの症例でもとの治療効果であるMR4.5(BCR-ABL IS≦0.0032%)の回復が確認され、本プロトコールによるSTOP試験が安全であることが確認された。

2）CML212 CMR試験：慢性期CMLに対して18ヶ月までのCMRの達成率をニロチニブとダサチニブで比較する前方視的ランダム化比較試験

平成28年1月に目標症例450例の登録を完了し、主要評価項目である18ヶ月までのCMRの累積達成率を両薬剤で比較するために、試験治療を継続中である。

3）CML212 STOP（N-STOP216, D-STOP216試験）：2年間以上CMRを維持した慢性期CML症例に対するニロチニブとダサチニブの中止試験（N-STOP216とD-STOP216試験の2つの第Ⅱ相試験）

平成28年12月に近畿大学医学部の倫理委員会の承認を得て、両試験とも平成29年1月から症例登録を開始し、3月末時点で両試験共に22施設の倫理委員会で承認され、N-STOP216試験に5例、D-STOP216試験に8例の症例登録があった（両試験とも目標登録症例数は50例）。

2.基礎研究の進捗状況

1）TKIを中止できる症例の選択法の確立

STIM213試験においてTFR維持症例と再発症例において、イマチニブ中止前と中止後1、3ヶ月目の末梢血T/NK細胞のプロファイルを比較し、TTFR達成群と再発例において抗腫瘍免疫能に関するNK/T細胞の動態に違いがあることを明らかにした。

2)全エクソン解析によるCML細胞における遺伝子変異の解析

24例の初発慢性期CML症例の末梢血単核球DNAを用いて全エクソン解析を行い、体細胞突然変異を解析した。合計で184の遺伝子に191箇所の変異を認め、1症例あたりの変異数中央値は8個であった(range 1-17)。年齢, Hb濃度, 白血球数が遺伝子変異数と有意に相関した。特にエピジェネティック制御因子であるASXL1, TET2, TET3, KDM1A, MSH6の変異を25%の高頻度で認めた。その他, 細胞分裂またはシグナル伝達に関連する遺伝子の変異が多く認められた。以上の結果から, これら初発時に同定された遺伝子変異はBCR-ABLに加えて, CML発症に強く関与していることが明らかとなった。本研究結果はBlood Cancer Journal誌 2017 Apr 28;7(4):e559.に公表した。

2)CML細胞における遺伝子変異と治療反応性についての解析

CMLにおけるTKI治療反応性と関連する遺伝子変異を検索する目的で、European LeukemiaNet CMLの治療効果判定基準でfailureもしくはWarningに該当した15症例で骨髄性腫瘍において高頻度に認められる54遺伝子を対象に遺伝子変異解析を行った。その結果、いくつかの遺伝子変異が同定され、これら遺伝子変異とTKIの治療反応性との関連が示唆された。

3) CML幹細胞の解析および抗腫瘍免疫能の解析

TKI阻害剤治療中の患者骨髄/末梢血に残存するCML細胞や免疫担当細胞の解析を施行した。残存CML幹細胞に対する抗腫瘍免疫に関与する細胞集団を同定した。また、アロステリック阻害剤、ヘッジホッグ阻害剤など治癒を目指した新規治療候補薬剤のCML幹細胞に対する効果やその作用機序の検討を継続した。

1. Progress of the clinical trials

1) STIM213 study: A phase II study to stop imatinib in patients with chronic myeloid leukemia (CML) in chronic phase, who maintained complete molecular response (CMR) for more than 2 years

We had already completed the enrollment of the patients, and all of the patients had stopped imatinib. The primary endpoint, treatment-free remission (TFR) rate at 12 months after imatinib discontinuation, was 69%. We are now following the patients, who remain in TFR without imatinib treatment. For the patients, who relapsed after imatinib discontinuation, we restarted imatinib promptly and consequently most of the patients recovered CMR, indicating that this protocol is safe for stopping imatinib.

2) CML212 CMR study : A prospective randomized trial to compare the cumulative achievement of CMR between nilotinib and dasatinib in patients with CML in chronic phase

We had already completed the enrollment of 450 patients in January, 2016. We are now following the patients to evaluate the primary endpoint.

3) CML212 STOP study (N-STOP216 and D-STOP216 studies): Two phase II trails to stop nilotinib or dasatinib in CML patients in chronic phase, who maintained CMR for more than 2 years

These two studies were started in JALSG from January, 2017. By the end of March, 2017, these studies were admitted by the institutional review board in 22 centers, and five patients were enrolled in N-STOP216 study and eight patients in D-STOP216 study (50 patients are planned to be registered in each study).

2. Progress of the basic research

1) Characteristics of the difference in profiles of NK/T cells between the patients who maintain CMR and those who relapsed

We compared the profiles of NK/T cells between the patients who maintained TFR and those who relapsed at three time points (before and after 1 and 3 months imatinib discontinuation). As a result, we found that the kinetics of some NK/T cell populations is different between two groups.

2) Whole exon analysis to detect point mutations in CML cells

We conducted whole exon analysis in 24 untreated CML patients and found 191 point mutations in 184 genes. CML cells in each patient had point mutations with a median number of 8 (range 1-17). Mutations of ASXL1, TET2, TET3, KDM1A, MSH6 genes were observed in about 25% of the analyzed patients. Also, mutations were detected in genes, which regulate cell division or signal transduction. The number of mutations were correlated with age, Hb concentration, and WBC count, suggesting that these mutations would play some role in the pathogenesis of CML together with a causative gene, BCR-ABL These results were published in Blood Cancer Journal 2017 Apr 28;7(4):e559.

3) The significance of point mutations in the treatment response to tyrosine kinase inhibitors (TKIs)

We analyzed mutational status of 54 genes, which are known to be involved in the pathogenesis of myeloid malignancies such as acute myeloid leukemia and myelodysplastic syndromes, in 15 patients showing resistance to TKI. As a result, we found several mutations that would cause the resistance to TKIs.

4) Characterization of CML stem cells and analysis of the immune responses to these cells

We characterized residual CML stem cells during TKI treatment. Also, we analyzed the immune reactions to these residual CML stem cells and identified some population that acts on CML stem cells as an immune target. In addition, to construct novel therapeutic strategies to cure CML, we analyzed the effects of allosteric inhibitors and Hedgehog inhibitors on CML stem cells.

Ⅲ. 成果の外部への発表

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（2）学会・シンポジウム等における口頭・ポスター発表

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（3）「国民との科学・技術対話社会」に対する取り組み

なし

（4）特許出願