

様式第19

学会等発表実績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導治験に関する研究」

機関名 福岡大学

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Is watch and wait still standard for indolent ATL? (口頭発表)	Ishitsuka K.	7th annual T-cell lymphoma forum	Jan. 29-31, 2015	国外
A retrospective study of the patients with chronic- and smoldering-type adult T-cell leukemia-lymphoma in Japan. (口頭発表)	Katsuya H, Ishitsuka K, Amano M, Kawai K, Hino R, Utsunomiya A, Hanada S, Yamanaka T, Suzumiya J, Tamura K.	第12回日本臨床腫瘍学会学術集会	2014年7月18日	国内

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma.	Ishitsuka K, Tamura K.	Lancet Oncol.	15(11):e517-26, 2014	国外
Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A).	Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K, Tsukasaki K.	Br J Haematol.	166(5):739-48, 2014	国外

Promise of combining a Bcl-2 family inhibitor with bortezomib or SAHA for adult T-cell leukemia/lymphoma.	Kunami N, Katsuya H, Nogami R, Ishitsuka K, Tamura K.	Anticancer Res.	34(10):5287-94, 2014	国外
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様式第 19

学 会 等 発 表 実 績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導治験に関する研究」

機関名 公益財団法人慈愛会 今村病院分院

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
なし				

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Influence of human T-lymphotropic virus type 1 coinfection on the development of hepatocellular carcinoma in patients with hepatitis C virus infection.	Tokunaga M, Uto H, Oda K, Tokunaga M, Mawatari S, Kumagai K, Haraguchi K, Oketani M, Ido A, Ohnou N, Utsunomiya A, Tsubouchi H	J Gastroenterol	Dec, 2014	国内
Japan Clinical Oncology Group prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A).	Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K, Tsukasaki K	Br J Haematol	Sep, 2014	国外

Recent advances in treatment of adult T-cell leukemia- lymphomas.	Utsunomiya A, Choi I, Chihara D, Seto M	Cancer Science	2015 (in press)	国内
Clinical outcomes of a novel therapeutic vaccine with Tax peptide-pulsed dendritic cells for adult T cell leukaemia/lymphoma in a pilot study.	Suehiro Y, Hasegawa A, Iino T, Sasada A, Watanabe N, Matsuoka M, Takamori A, Tanosaki R, Utsunomiya A, Choi I, Fukuda T, Miura O, Takaishi S, Teshima T, Akashi K, Kannagi M, Uike N, Okamura J	Br J Haematol	2015 (in press)	国外

様式第19

学会等発表実績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導治験に関する研究」

機関名 鹿児島大学病院

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
In vitro and in vivo effect of ATO/IFN/AZT for adult T cell leukemia/lymphoma. (ポスター発表)	Hachiman M, Yoshimitsu M, Kuroki A, Nakamura D, Arima N	ミラノ、イタリア、European Hematology Association	2014年6月	国外

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
CD160 expression defined a uniquely exhausted subset of T lymphocytes in HTLV-1 infection.	Ezinne CC, Yoshimitsu M, Arima N.	Biochem Biophys Res Commun. (453):379-384.	2014年11月	国外
A retrospective analysis of treatment outcomes in aggressive adult T cell leukemia/lymphoma patients treated with or without allogeneic stem cell transplantation: A single center experience.	Kawada H, Yoshimitsu M, Nakamura D, Arai A, Hayashida M, Kamada Y, Maekawa K, Fujino S, Arima M, Arima N, Tabuchi T, Inoue H, Hamda H, Suzuki S, Matsushita K, Arima N.	Biology of Blood and Marrow Transplantation.	2014年12月	国外

様式第19

学会等発表実績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導治験に関する研究」

機関名 名古屋市立大学

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Reactivation of hepatitis B virus (HBV) in HBV-resolved patients with adult T-cell leukemia/lymphoma (Oral presentation)	Totani H, Kusumoto S, Ishida T, Ito A, Ri M, Komatsu H, Ueda R, Tanaka Y, Niimi A, Iida S.	The 12th Annual Meeting of Japanese Society of Clinical Oncology	18-Jul-14	国内

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Dose-intensified chemotherapy alone or in combination with mogamulizumab in newly diagnosed aggressive ATL: a randomized phase II study.	Ishida T, Jo T, Takemoto S, Suzushima H, Uozumi K, Yamamoto K, Uike N, Saburi Y, Nosaka K, Utsunomiya A, Tobinai K, Fujiwara H, Ishitsuka K, Yoshida S, Taira N, Moriuchi Y, Imada K, Miyamoto T, Akinaga S, Tomonaga M, Ueda R.	Br J Haematol.	2015, in press	国外

様式第19

学会等発表実績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導試験に関する研究」

機関名 長崎大学

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Clinical significance of overexpression of MALT1 in adult T-cell leukemia/lymphoma. (口頭発表)	新野大介、 谷口広明、 今泉芳孝、 佐々木大介、 長谷川寛雄、 三好寛明、 郭英、 加藤丈晴、 柳原克紀、 宮崎泰司、 大島孝一	第76回日本血液学会学術集会	2014/10/31	国内
A nationwide survey of patients with adult T cell leukemia/lymphoma (ATL) in Japan: 2010-2011. (口頭発表)	野坂生郷、 岩永正子、 石澤賢一、 石田陽治、 内丸薫、 石塚賢治、 天野正宏、 石田高司、 今泉芳孝、 鶴池直邦、 宇都宮與、 大島孝一、 河井一浩、 田中淳司、 戸倉新樹、 飛内賢正、 渡邊俊樹、 塚崎邦弘	第76回日本血液学会学術集会	2014/11/1	国内
Maintenance therapy in elderly patients with adult T-cell leukemia-lymphoma. (ポスター発表)	加藤丈晴、 今泉芳孝、 谷口広明、 牧山純也、 上条玲奈、 北之園英明、 小林裕児、 田口正剛、 松尾真稔、 安東恒史、 澤山靖、 新野大介、 田口潤、 今西大介、 波多智子、 大島孝一、 宮崎泰司	第76回日本血液学会学術集会	2014/11/1	国内

Analysis of acute crisis of smoldering and chronic adult T-cell leukemia-lymphoma. (ポスター発表)	谷口広明、今泉芳孝、高崎由美、北之園英明、中島潤、加藤丈晴、牧山純也、安東恒史、澤山靖、今西大介、田口潤、長谷川寛雄、波多智子、塚崎邦弘、宮崎泰司	第76回日本血液学会学術集会	2014/10/31	国内
末梢血と肝臓の病変で発症し indolentな経過をたどった成人T細胞白血病リンパ腫 (ポスター発表)	谷口広明、今泉芳孝、北之園英明、加藤丈晴、牧山純也、安東恒史、澤山靖、今西大介、田口潤、波多智子、長谷川寛雄、新野大介、大島孝一、宮崎泰司	第54回日本リンパ網内系学会総会	2014/6/21	国内

2. 学会誌・雑誌等における論文掲載

掲載した論文 (発表題目)	発表者氏名	発表した場所 (学会誌・雑誌等名)	発表した時期	国内・外の別
Molecular analysis of loss of CCR4 expression during mogamulizumab monotherapy in an adult T cell leukemia/lymphoma patient.	Taguchi M, Imaizumi Y, Sasaki D, Higuchi T, Tsuruda K, Hasegawa H, Taguchi J, Sawayama Y, Imanishi D, Hata T, Yanagihara K, Yoshie O, Miyazaki Y.	Ann Hematol. [Epub ahead of print]	2014 Oct 23	国外

Heat shock protein 90 inhibitor NVP-AUY922 exerts potent activity against adult T-cell leukemia-lymphoma cells.	Taniguchi H, Hasegawa H, Sasaki D, Ando K, Sawayama Y, Imanishi D, Taguchi J, Imaizumi Y, Hata T, Tsukasaki K, Uno N, Morinaga Y, Yanagihara K, Miyazaki Y.	Cancer Sci. 105(12):1601-8.	2014 Dec	国外
Treatment outcome of elderly patients with aggressive adult T cell leukemia-lymphoma: Nagasaki University Hospital experience.	Makiyama J, Imaizumi Y, Tsushima H, Taniguchi H, Moriwaki Y, Sawayama Y, Imanishi D, Taguchi J, Hata T, Tsukasaki K, Miyazaki Y.	Int J Hematol. 100(5):464-72.	2014 Nov	国外
Molecular characterization of chronic-type adult T-cell leukemia/lymphoma.	Yoshida N, Karube K, Utsunomiya A, Tsukasaki K, Imaizumi Y, Taira N, Uike N, Umino A, Arita K, Suguro M, Tsuzuki S, Kinoshita T, Ohshima K, Seto M.	Cancer Res. 74(21):6129-38.	2014 Nov 1	国外

<p>Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A).</p>	<p>Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K, Tsukasaki K.</p>	<p>Br J Haematol. 166(5):739-48.</p>	<p>2014 Sep</p>	<p>国外</p>
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様式第 19

学 会 等 発 表 実 績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導試験に関する研究」

機関名：独立行政法人国立病院機構九州がんセンター

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Unrelated bone marrow transplantation with reduced intensity conditioning regimen for elderly patients with adult T-cell leukemia/lymphoma, feasibility study with two year follow up data. (Poster)	Choi I, Eto T, Tanosaki R, Shimokawa M, Takatsuka Y, Utsunomiya A, Takemoto S, Taguchi J, Fukushima T, Kato K, Teshima T, Nakamae H, Suehiro Y, Yamanaka T, Okamura J, Uike N.	19th Congress Of The European Hematology Association (Milan, Italy)	14-Jun-14	国外
Allogeneic hematopoietic cell transplantation for adult T cell leukemia/lymphoma. (Workshop)	Choi I, Uike N.	12th Annual Meeting of Japanese Society of Clinical Oncology (Fukuoka)	17-Jul-14	国内
Allogeneic Peripheral Blood Stem Cell Transplantation Using Reduced-Intensity Conditioning Regimen with Fludarabine and Busulfan from HLA-Matched Related Donor for Elderly Adult T-Cell Leukemia/Lymphoma: Results of Multicenter Phase II Study (ATL-NST-3). (Poster)	Tanosaki R, Choi I, Shimokawa M, Utsunomiya A, Tokunaga M, Nakano N, Fukuda T, Nakamae H, Takemoto S, Kusumoto S, Tomoyose T, Sueoka E, Shiratsuchi M, Suehiro Y, Yamanaka T, Okamura J, Uike N.	56th American Society of Hematology Annual Meeting and Exposition (San Francisco, CA)	7-Dec-14	国外

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所 (学会誌・雑誌等名)	発表した時期	国内・外の別
Treatment of patients with adult T cell leukemia/lymphoma with cord blood transplantation: a Japanese nationwide retrospective survey.	Kato K, Choi I, Wake A, Uike N, Taniguchi S, Moriuchi Y, Miyazaki Y, Nakamae H, Oku E, Murata M, Eto T, Akashi K, Sakamaki H, Kato K, Suzuki R, Yamanaka T, Utsunomiya	Biol Blood Marrow Transplant.	2014	国外
Potential contribution of a novel Tax epitope-specific CD4+ T cells to graft-versus-Tax effect in adult T cell leukemia patients after allogeneic hematopoietic stem cell transplantation.	Tamai Y, Hasegawa A, Takamori A, Sasada A, Tanosaki R, Choi I, Utsunomiya A, Maeda Y, Yamano Y, Eto T, Koh KR, Nakamae H, Suehiro Y, Kato K, Takemoto S, Okamura J, Uike N, Kannagi M.	J Immunol.	2013	国外

様式第 19

学 会 等 発 表 実 績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導試験に関する研究」

機関名 熊本大学医学部附属病院

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
A nationwide survey of patients with adult T cell leukemia-lymphoma (ATL) in Japan: 2010-2011. (口頭発表)	Nosaka K, Iwanaga M, Ishizawa K, Ishida Y, Uchimaru K, Ishitsuka K, Amano M, Ishida T, Imaizumi Y, Uike N, Utsunomia A, Ohshima K, Kawai K, Tanaka T, Tokura Y, Tobinai K, Watanabe T, Tsukasaki K.	大阪（第76回日本血液学会総会）	2014. 11	国内

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Japan Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leukaemia-lymphoma (JCOG0902A).	Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K,	Br J Haematol	166: 739-48, 2014	国外

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学 会 等 発 表 実 績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導試験に関する研究」

機関名 大分大学医学部

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
「移植医療と感染症」/ 同種造血細胞移植と感染症（口頭）	緒方正男	第88回日本感染症学会学術集会	2014/6/20	国内
Hypofibrinogenemia associated with steroid therapy in patients who developed GVHD after HSCT (ポスター)	Moroga Y, Ogata M, Yoshida N, Takata H, Nagamatsu K, Nashimoto Y, Takano K, Saburi Y, Kohoo K, Ikebe T, Shirao K	第76回日本血液学会学術集会	2014/11/1	国内

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Risk factors for human herpesvirus 6 reactivation and its relationship with syndrome of inappropriate antidiuretic hormone secretion after stem cell transplantation in pediatric patients.	Toriumi N, Kobayashi R, Yoshida M, Iguchi A, Sarashina T, Okubo H, Suzuki D, Sano H, Ogata M, Azuma H.	J Pediatr Hematol Oncol	Jun-14	国外
同種造血細胞移植後のHHV-6再活性化と脳炎	緒方正男	血液内科	2014年5月	国内
HHV-6A and HHV-6B in recipients of hematopoietic cell transplantation	Zerr DM, Ogata M.	Human Herpesviruses HHV-6A, HHV-6B & HHV-7, Diagnosis and Clinical Management, third edition	Jun-14	国外
Chest HRCT findings in acute transformation of adult T-cell lymphoma/leukemia.	Okada F, Sato H, Omeri AK, Ono A, Tokuyama K, Ando Y, Matsumoto A, Ogata M, Kohno K, Takano K, Mori H.	Eur Radiol. 11.	2015 Jan	国外

様式第19

学会等発表実績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導試験に関する研究」

機関名 日本赤十字社長崎原爆病院

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Cytotoxic T-lymphocyte analysis of aggressive types of adult T-cell leukemia/lymphoma patients with complete remission after intensive combination chemotherapy. (ポスター発表)	Jo T, Horio K, Shigematsu K.	San Francisco, USA (American Society of Hematology annual meeting)	2014. 12. 6	国外

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Extensive and destructive invasion of adult T-cell leukemia/lymphoma cells into systemic muscular tissues.	Jo T, Shigematsu K.	Blood	2014. 9. 4	国外

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学 会 等 発 表 実 績

委託業務題目「成人T細胞白血病・リンパ腫(ATL)に対する新規治療を開発する医師主導試験に関する研究」

機関名 佐世保市立総合病院

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
成人T細胞白血病・リンパ腫症例における同種造血幹細胞移植後再発時の浸潤臓器の後方視的検討（口頭発表）	糸永英弘、 田口潤、 谷口広明、 牧山純也、 澤山靖、 今泉芳孝、 吉田真一郎、 福島卓也、 森内幸美、 宮崎泰司	日本造血細胞移植学会 総会	2014	国内
再発・難治性成人T細胞白血病リンパ腫に対するモガムリズマブの治療成績に関する臨床的検討（ポスター発表）	谷口広明、 今泉芳孝、 北之園英明、 加藤丈晴、 田口正剛、 蓬萊真喜子、 牧山純也、 佐藤信也、 安東恒史、 澤山靖、 今西大介、 田口潤、 長谷川寛雄、 波多智子、 吉田真一郎、 森内幸美、 宮崎泰司	日本内科学会総会	2014	国内

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Treatment of Patients with Adult T Cell Leukemia/Lymphoma with Cord Blood Transplantation: A Japanese Nationwide Retrospective Survey.	Kato K, Choi I, Wake A, Uike N, Taniguchi S, Moriuchi Y, Miyazaki Y, Nakamae H, Oku E, Murata M, Eto T, Akashi K, Sakamaki H, Kato K, Suzuki R, Yamanaka T, Utsunomiya A.	Biol Blood Marrow Transplant.	2014	国外
Japana Clinical Oncology Group (JCOG) prognostic index and characterization of long-term survivors of aggressive adult T-cell leuaemia-lymphoma (JCOG0902A).	Fukushima T, Nomura S, Shimoyama M, Shibata T, Imaizumi Y, Moriuchi Y, Tomoyose T, Uozumi K, Kobayashi Y, Fukushima N, Utsunomiya A, Tara M, Nosaka K, Hidaka M, Uike N, Yoshida S, Tamura K, Ishitsuka K, Kurosawa M, Nakata M, Fukuda H, Hotta T, Tobinai K, Tsukadsaki K.	Br J Haematol.	2014	国外

IV. 研究成果の刊行物・別刷



Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma

Kenji Ishitsuka, Kazuo Tamura

Adult T-cell leukaemia-lymphoma (ATL) is a malignancy of peripheral T lymphocytes caused by human T-lymphotropic virus type I (HTLV-1), and its prognosis is poor. There are an estimated 5 million to 20 million HTLV-1 infected individuals worldwide; their lifetime risk of developing ATL is 3–5%, and high HTLV-1 proviral loads have been shown to be an independent risk factor. Recent advances in the treatment of ATL are the introduction of treatment targeted against CC chemokine receptor 4 (CCR4), which is abundantly expressed on most ATL cells, and allogeneic haemopoietic stem-cell transplantation for aggressive ATL. Promising outcomes are also reported with early intervention for indolent ATL with interferon α and zidovudine. Clinical trials should incorporate a validated prognostic index to assess the results, because of the difficulties associated with undertaking large-scale trials and significant diversity of clinical features with ATL, even in the same clinical subtypes (acute, lymphoma, chronic, and smoldering).

Introduction

Adult T-cell leukaemia-lymphoma (ATL) is a malignancy of peripheral T lymphocytes caused by human T-lymphotropic virus type I (HTLV-1), and its prognosis is poor compared with other aggressive non-Hodgkin lymphomas. The clinical entity of ATL was first proposed in 1977 as a distinct T-cell neoplasm frequently observed in southwestern Japan, and the RNA retrovirus HTLV-1 was subsequently isolated as the causative virus.^{1,2} HTLV-1 also causes HTLV-1-associated myelopathy-tropical spastic paraparesis (HAM-TSP), a chronic inflammatory disease of the CNS characterised by slowly progressive spastic paraparesis, lower limb sensory disturbance, and bladder or bowel dysfunction.^{3,4} Differences in the immune response to HTLV-1 in infected individuals, which are at least partially dependent on the HLA haplotypes—ie, low immune responders to HTLV-1 infected cells are at risk of ATL but high immune responders to HTLV-1 infected cells are at risk of HAM-TSP—have been proposed as the reasons why the same virus causes two distinctive diseases, one a malignant disease and the other an inflammatory disease.^{5,6} By contrast, a less efficient response by cytotoxic T cells against HTLV-1 is reported to be the cause of risk of HAM-TSP since it causes a higher proviral load and higher antigen expression that activates and expands antigen-specific T-cell responses, followed by induction of large amount of proinflammatory cytokines and chemokines.⁷ In HTLV-1 carriers in Japan, the lifetime risk of ATL is estimated 3–5% (5–7% for men and 2–4% for women) and of HAM-TSP is 0·25%.^{8,9}

The clinical course of ATL is very heterogeneous, and the Japan Clinical Oncology Group (JCOG) has proposed four clinical subtypes (acute, lymphoma, chronic, and smoldering types) based on the prognostic factors, clinical features, and the natural history of the disease. Acute, lymphoma, and unfavourable chronic types are considered to be aggressive ATLs, and favourable chronic and smoldering types are indolent ATLs.^{10,11}

In this Review, we discuss the epidemiology of HTLV-1, transmission of HTLV-1 and its prevention, recent advances in the oncogenesis and pathophysiology of ATL, identification of HTLV-1 carriers at high risk of development of ATL, and the clinical features, treatment, and prognostic index of this disease.

Epidemiology of HTLV-1

HTLV-1 is endemic in southwestern Japan, the Caribbean, intertropical Africa, the Middle East, South America, and Papua New Guinea, and the prevalence of patients with ATL and HAM-TSP has been linked to the distribution of HTLV-1.¹²

The origin of HTLV-1 is considered to be primate T-cell lymphotropic virus (PTLV) in African non-human primates. It migrated within a simian reservoir towards Asia, and evolved into simian T-cell leukaemia virus type-I (STLV-1). This STLV-1 lineage spread to Japan and India, and Indonesia where it may have crossed the simian–human barrier for the first time, which resulted in the HTLV-1c (Australo-Melanesian) subtype. STLV-1 returned to Africa from Asia and evolved into several subtypes of HTLV-1a (the cosmopolitan subtype), 1b (the central African subtype), 1d, 1e, and 1f around 19 000 to 35 500 years ago. HTLV-1a arose in west Africa, and spread to the USA, Japan, the Middle East, and North Africa (known as HTLV-1a late) because of the slave trade and the increased mobility of human beings.¹³

An estimated 5 million to 20 million individuals are infected with HTLV-1 worldwide.^{14,15} In a study by Satake and colleagues,¹⁶ the seropositivity of HTLV-1 among first-time blood donors was reported to be 0·32% (3787 of 1196 321) in Japan between 2006 and 2007. Adjusted overall prevalences were estimated to be 0·66% in men and 1·02% in women, and the number of HTLV-1 carriers aged 0–99 years is estimated to be at least 1·08 million in Japan, which is 10% lower than reported in the 1988 database cited in their article.¹⁶ Most carriers are aged 70–80 years; this finding differs from that reported in the 1988 database, in which the most carriers were aged

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50–60 years. A marked decrease in the prevalence of HTLV-1 based on the age of the blood donor has been reported. For example, the mean carrier rate for all donors in one prefecture located in southwestern Japan was 1.95%, whereas the rate was 8.7% in men aged 60–64 years, and 14.0% in women aged 60–64 years. Sex differences in HTLV-1 prevalence increase after age 20 years, with more women infected than men.¹⁶ In Brazil, the prevalence of HTLV-1 among first-time blood donors was 0.14% (363 of 281760) between 2007 and 2009, and was significantly correlated with age (adjusted odds ratio [aOR] 5.23 for age >50 *vs* <20 years), female sex (aOR 1.97), and black (aOR 2.70 *vs* white) and mixed race (aOR 1.78 *vs* white), and inversely correlated with education (aOR 0.49, college graduates *vs* those who did not complete high school).¹⁷ By contrast, a study showed that the prevalence of HTLV-1 in first-time blood donors in European countries was 0–0.0048%, except for Romania, where it was 0.05%.^{18–20} Most HTLV-1 infected donors in these countries were either from an endemic area or had a sexual partner from an endemic area.¹⁸

Transmission and prevention of HTLV-1

Clustering of HTLV-1 carriers was reported in family members of patients with ATL soon after the identification of the virus, suggesting that this virus is transmitted by close contact within the family.^{21,22} Three major HTLV-1 transmission routes are mother-to-child, sexual intercourse, and blood transfusions containing cellular components—ie, HTLV-1 infected lymphocytes.²³

Transmission via transfusion has been almost eliminated through viral screening of donated blood, which has been done since 1986 in Japan, 1988 in the USA, 1991 in France, 1993 in Brazil, and 2002 in the UK. However, some European countries have not introduced screening, and Norway and Finland decided to stop screening because no positive donors were found after 7 and 13 years of testing, respectively.¹⁸

Sexual transmission is mainly male to female via HTLV-1-infected lymphocytes in semen, and can be prevented by use of a latex condom. Although the prevalence of HTLV-1 in the husbands of HTLV-1 carrier wives was not higher than that in the general population, the wives of carrier husbands in elderly populations were almost invariably infected.²¹ The prevalence of HTLV-1 increases in women in an age-dependent manner after they reach their 20s, which supports the male-to-female transmission of HTLV-1; however, individuals infected with HTLV-1 after adolescence are considered to be at very low risk of developing ATL. Therefore, mother-to-child transmission is currently the most important risk factor of HTLV-1 infection associated with the subsequent development of ATL. A Japanese long-term prospective study²⁴ reported HTLV-1 transmission rates from infected mother to child of 20.5% after the child was breastfed at least 6 months, of 8.3% after breastfeeding for less than 6 months, and of 2.4% when exclusively

formula-fed. On the basis of these findings, a nationwide programme to prevent mother-to-child infection was initiated in Japan in April, 2011, by screening all pregnant women for HTLV-1 infection and recommending either exclusive formula feeding, freeze-thawing of expressed breast milk to destroy HTLV-1-infected lymphocytes, or breastfeeding for a maximum of 3 months if the mother is infected, unless they give birth to high-risk infants such as premature babies.

Oncogenesis and pathophysiology of ATL

HTLV-1-infected cells express the virus protein Tax, which has various cellular functions including activation of NF- κ B, Akt signalling, and cyclin-dependent kinases, and silencing of P53 function. Tax has been considered to play a key part in the oncogenesis of ATL in the early stages, because Tax could immortalise T lymphocytes *in vitro*,²⁵ and transgenic mice which expressed Tax showed oncogenic capabilities.²⁶ However, because Tax is a target for the host cytotoxic T cells, there is some survival advantage for Tax expression to be impaired to enable HTLV-1-infected cells to escape immune surveillance and survive in the host.²⁷ Studies have shown that Tax transcript could not be detected in fresh ATL cells derived from more than half of patients with this disease because of the accumulation of non-sense mutations, insertions and deletion in Tax, silencing of viral transcription by DNA methylation of the provirus, or deletion of the proviral 5' LTR.²⁷ It suggests the possibility that Tax is not necessarily important to develop ATL in the late stage of oncogenesis.

The universal expression of HTLV-1 basic leucine zipper (HBZ), an antisense mRNA transcribed from the 3' LTR, has been reported in fresh ATL cells and HTLV-1-infected cells.²⁷ The suppression of HBZ gene transcription inhibits the proliferation of ATL cells, while expression of HBZ gene promoted the proliferation of a human T cell line *in vitro*.²⁸ HBZ selectively inhibits classic NF- κ B pathways without inhibiting alternative NF- κ B pathways. Moreover, HBZ induced the expression of FOXP3 in naive T cells, which is consistent with one of the established characteristic phenotypes of ATL cells.^{29,30} These findings strongly suggest that HBZ and Tax play an important part in the oncogenesis of ATL by HTLV-1.

The suppression of ATL cell growth and promotion of apoptosis by inhibition of NF- κ B with miR-31 have been reported *in vitro*.³¹ Repression of miR-31, which negatively regulates NF- κ B signalling by inhibiting NF- κ B-inducing kinase (NIK), was confirmed by profiling cellular microRNA on primary ATL cells. Therefore, the activation of NIK by genetic and epigenetic loss of miR-31 has been suggested as a possible mechanism for the constitutive activation of NF- κ B in ATL cells that are not expressing Tax.³¹

An analysis using oligoarray comparative genomic hybridisation against paired samples with acute-type ATL