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血液腫瘍内科領域の診療における最新の話題 Diffuse Large B Cell Lymphoma 口頭	吉田功	岡山 内科レジデントカンファレンス2014	2014.10.18	

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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
Cefozopran, meropenem, or imipenem-cilastatin compared with cefepime as empirical therapy in febrile neutropenic adult patients: A multicenter prospective randomized trial	Nakane T, Tamura K, Hino M, Tamaki T, Yoshida I, Fukushima T, Tatsumi Y, Nakagawa Y, Hatanaka K, Takahashi T, Akiyama N, Tanimoto M.	Journal of Infection and Chemotherapy	21 (2015) 16-22	
「再発・治療抵抗性びまん性大細胞型B細胞リンパ腫」	吉田功	プリンシプル血液疾患の臨床 リンパ腫・骨髄腫の最新療法 中山書店	2014年	

様式第１９

学 会 等 発 表 実 績

委託業務題目「高齢者多発性骨髄腫患者に対する至適な分子標的療法の確立と治療効果および有害事象を予測するバイオマーカーの探索的研究」

機関名埼玉医科大学総合医療センター

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
Targeting Wnt/β-catenin signaling pathway in multiple myeloma,口頭	Takayuki Tabayash	第76回日本血液学会学術総会	2014/10/31	国内
Targeting the Wnt/β-Catenin Signaling Pathway in Multiple Myeloma: A Possible New Therapeutic Approach to Overcome Bortezomib-Resistance. ポスター	Takayuki Tabayash	第56回米国血液学会	2014/12/7	国外

２．学会誌・雑誌等における論文掲載

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様式第１９

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委託業務題目「高齢者多発性骨髄腫患者に対する至適な分子標的療法の確立と治療効果および有害事象を予測するバイオマーカーの探索的研究」

機関名　東北大学病院

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

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
Induction of thymic stromal lymphopoietin in mesenchymal stem cells by interaction with myeloma cells	Nakajima S, Fujiwara T, Ohguchi H, Onishi Y, Kamata M, Okitsu Y, Fukuhara N, Ishizawa K, Harigae H	Leukemia & lymphoma 55:2605-2613	20014.11	国外

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委託業務題目「高齢者多発性骨髄腫患者に対する至適な分子標的療法の確立と治療効果および有害事象を予測するバイオマーカーの探索的研究」

機関名　千葉県がんセンター　外来化学療法科　辻村秀樹

１．学会等における口頭・ポスター発表

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Interim analysis of an ongoing phase II trial assessing safety and efficacy of R-IDEA as salvage therapy in patients with relapsed/refractory DLBCL: An intergroup study of the society of lymphoma treatment in Japan (SoLT-J) and the west Japan hematology/oncology group (WestJHOG)（ポスター発表）	E. Kondo, K. Yamamoto, T. Masunari, K. Miura, J. Takizawa, Y. Masaki, T. Matsumura, Y. Hiramatsu, J. Murakami, H. Tsujimura, N. Tomita, Y. Maeda, M. Kanno	ESMO 2014 Congress	2014/9月	国外（スペイン）
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がん化学療法後の重篤な有害事象（SAE）の全症例登録と管理（口演;プレナリーセッション）	味八木寿子、辻村秀樹、山田みつぎ、鎌形幸子、中澤裕子、浅子恵利、石原優、熊谷匡也	第12回日本臨床腫瘍学会学術集会	2014/7月	国内（福岡）
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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
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学　会　等　発　表　実　績

委託業務題目「高齢者多発性骨髄腫患者に対する至適な分子標的療法の確立と治療効果および有害事象を予測するバイオマーカーの探索的研究」

機関名　福井大学医学部　岸慎治

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
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Febuxostat for Management of Tumor Lysis Syndrome Including its Effects on Levels of Purine Metabolites in Patients with Hematological Malignancies - A Single Institution's, Pharmacokinetic and Pilot Prospective Study.	Takai M, Yamauchi T, Ookura M, Matsuda Y, Tai K, Kishi S, Yoshida A, Iwasaki H, Nakamura T, Ueda T.	Anticancer Res.	2014年12月	国外
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IV. 研究成果の刊行物・別刷

Int J Hematol
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ORIGINAL ARTICLE

Phase 1 study in Japan of siltuximab, an anti-IL-6 monoclonal antibody, in relapsed/refractory multiple myeloma

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Abstract Siltuximab, a chimeric monoclonal antibody with high affinity and specificity for interleukin-6, has been shown to enhance anti-multiple myeloma activity of bortezomib and corticosteroid in vitro. We evaluated the safety, pharmacokinetics, immunogenicity, and antitumor effect of siltuximab in combination with bortezomib and dexamethasone in Japanese patients with relapsed or refractory multiple myeloma. This open-label, phase 1, dose-escalating study used two doses of siltuximab: 5.5 and 11.0 mg/kg (administered on day 1 of each 21-day cycle). In total, nine patients were treated. The most common grade 3/4 adverse events, lymphopenia (89 %) and thrombocytopenia (44 %), occurred in patients receiving both doses of siltuximab; however, no dose-limiting toxicities (DLTs) were observed. Following intravenous administration of siltuximab at 5.5 and 11.0 mg/kg, the maximum serum concentration and the area under the curve from 0 to 21 days and from 0 to infinity increased in an approximately dose-proportional manner. Mean half-life, total systemic clearance, and volume of distribution were similar at doses of 5.5 and 11.0 mg/kg. Across both doses, six of the nine patients had complete or partial response (22 and 44 %, respectively). In conclusion, as no DLT was observed, the recommended dose for this combination is 11.0 mg/kg once every 3 weeks. The study is registered at http://www.clinicaltrials.gov as NCT01309412.

Keywords Bortezomib · Dexamethasone · Interleukin 6 · Multiple myeloma · Siltuximab

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Introduction

Multiple myeloma is a B cell malignancy characterized by excessive malignant plasma cells in bone marrow as well as increased serum and urine monoclonal protein (M-protein) [1]. Clinical manifestations of multiple myeloma include bone disease, renal dysfunction, hypercalcemia, cytopenia, hyperviscosity, and peripheral neuropathy [2]. Proteasome inhibitors, such as bortezomib, have improved outcomes as induction and maintenance treatments, yet a majority of patients experience relapses and become refractory [3, 4].

The pleiotropic cytokine interleukin-6 (IL-6) is thought to play a central role in the pathogenesis of multiple myeloma. It is involved in the proliferation, differentiation, and

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survival of malignant plasma cells [5–7]. Siltuximab is a chimeric, human–murine, monoclonal antibody with high affinity and specificity for IL-6. It has been investigated through clinical studies in patients with multiple myeloma, Castleman's disease, and other lymphomas. In multicentric Castleman's disease, siltuximab, with a recommended dose of 11 mg/kg every 3 weeks, has shown evidence of efficacy by blocking IL-6 activity [8–10].

In vitro preclinical studies have demonstrated that the combination of siltuximab and bortezomib has an additive to a synergistic effect in inducing apoptosis in multiple myeloma cell lines. The cancer cells respond to the proapoptotic effects of proteasome inhibitors with survival pathways that can include antiapoptotic myeloid cell leukemia (Mcl)-1 protein and heat shock proteins (HSPs). IL-6 upregulates these pathways in myeloma cells, and reduction of IL-6 could reduce their interference with bortezomib's proapoptotic effects [11]. Overcoming IL-6-mediated cell resistance by an IL-6 antagonist may also augment the effectiveness of corticosteroids in treating multiple myeloma. IL-6 can protect multiple myeloma cells from apoptosis induced by corticosteroids and chemotherapeutics [12–15]. Siltuximab increased the sensitivity of myeloma cells to dexamethasone in vitro, and in combination with dexamethasone, reduced patient tumor cell viability [12, 16].

Given the preclinical results, anti-IL-6-directed treatment is a logical addition to bortezomib and dexamethasone. The current study was conducted in Japan to evaluate the safety and tolerability of siltuximab up to 11.0 mg/kg in combination with bortezomib and dexamethasone in patients with relapsed/refractory multiple melanoma. Additionally, the pharmacokinetics (PK), immunogenicity, and preliminary efficacy of siltuximab were evaluated.

Materials and methods

Study design

This was a nonrandomized, open-label, dose-escalating, phase 1 study in patients who had relapsed/refractory multiple myeloma (http://www.clinicaltrials.gov; NCT01309412). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices and was approved by the institutional review board at each participating institution. Two doses of siltuximab were evaluated: 5.5 and 11.0 mg/kg. The initial siltuximab dose level of 5.5 mg/kg, which is lower than the maximum dose in earlier dose-finding studies [10, 17], was selected for this study from a safety standpoint. The rationale for selecting siltuximab 11.0 mg/kg every 3 weeks was due to previous findings of effective response rates in patients with Castleman's disease [4]. Siltuximab was administered intravenously over 1 h on day 1, after administration of bortezomib and dexamethasone during a 21-day cycle. Bortezomib was administered intravenously at 1.3 mg/m^2 on days 1, 4, 8, and 11 of each cycle, followed by a 10-day rest period. In the ninth or subsequent cycles of treatment, bortezomib was administered once weekly (days 1 and 8) followed by a 13-day rest period (days 9–21). Dexamethasone was administered orally at 20 mg four times weekly (days 1, 2, 4, 5, 8, 9, 11, and 12) with a 9-day rest period. In the ninth or subsequent cycles of treatment, the dosing regimen for dexamethasone was changed to twice-weekly oral administration of 10 mg (days 1, 2, 8, and 9) followed by a 12-day rest period (days 10–21). After the recommended dose of 11.0 mg/kg was determined, those patients whose starting dose was 5.5 mg/kg and who had not achieved complete response (CR) were escalated to 11.0 mg/kg in the next cycle based on the patient's willingness to proceed and the investigator's discretion. This study was not designed to estimate the maximum tolerated dose. Doses were withheld or reduced if patients could not tolerate therapy (Table 1). Administration was repeated in cycles of 21 days until disease progression. Up to 15 patients were planned for enrollment in the study: up to six patients were considered for the 5.5 mg/kg dose and up to nine patients were considered for the 11.0 mg/kg dose.

Eligibility

Eligible patients had to be 20 years of age or older, have symptomatic or nonsecretory multiple myeloma according to the International Myeloma Working Group criteria [18], have previously received 1–3 treatments for multiple

Table 1 Treatment withheld or reduced

Treatment	First dose reduction	Second dose reduction
Siltuximab (all cycles)	No dose reduction allowed*	–
Bortezomib 1.3 mg/m^2 (all cycles)	Bortezomib 1.0 mg/m^2	Bortezomib 0.7 mg/m^2
Dexamethasone 20 mg (cycles 1–8)	Dexamethasone 10 mg	No (further) dose reduction allowed*
Dexamethasone 10 mg (cycles ≥9)	No dose reduction allowed*	–

*As no dose reduction was allowed, protocol was to discontinue all the therapies (siltuximab, bortezomib, and dexamethasone)

myeloma and had relapsed or been refractory (less than minimal response, or disease progression within 2 months of last dose) after the most recent regimen. Patients were also included if they had a measurable lesion (generally, serum immunoglobulin G [IgG] or serum immunoglobulin M [IgM] M-protein ≥1.0 g/dL; serum immunoglobulin A [IgA] M-protein ≥0.5 g/dL; serum immunoglobulin D [IgD] M-protein ≥0.05 g/dL; or serum immunoglobulin E [IgE] M-protein ≥50 IU/mL). For nonsecretory multiple myeloma, measurable lesions were defined as patients with a soft tissue mass (plasmacytoma) that could be measured in two dimensions as longest diameter ≥2 cm with an appropriate diagnostic imaging technique (computed tomography or magnetic resonance imaging). Additionally, patients were eligible if they had an Eastern Cooperative Oncology Group performance status of 0–2; adequate hematologic function (absolute neutrophil count ≥1,000/mm^3, hemoglobin ≥8 g/dL, platelet count ≥50,000/mm^3); adequate hepatic function (aspartate aminotransferase and alanine aminotransferase ≤2.5 times the upper limit of normal, total bilirubin ≤1.5 mg/dL); corrected serum calcium <12.5 mg/dL; and adequate renal function (creatinine clearance [CrCL] ≥20 mL/min).

Patients were excluded if they had a condition in which M-protein was present in the absence of a clonal plasma cell infiltration with lytic bone lesions; peripheral neuropathy (grade 1 with pain or ≥ grade 2); previous IL-6 therapy; previous poor response to bortezomib due to its toxicity; an allogeneic stem cell transplantation within 28 days prior to study treatment; or major surgery, chemotherapy, plasmapheresis, or radiation therapy within 21 days before study treatment. Patients who had significant respiratory illnesses (pneumonitis, interstitial pneumonia, or pulmonary fibrosis); significant cardiac disease; significant concomitant illnesses (including human immunodeficiency virus); or any condition that the investigators found inappropriate were also excluded. Concomitant therapy with other anticancer therapies, live attenuated vaccines, systemic corticosteroids, or other therapies the investigators found unsuitable were not allowed. Informed consent was obtained from each patient before study enrollment.

Assessment of safety

Safety evaluations included adverse events (AEs); laboratory tests (hematology, blood chemistry, lipid panel, urinalysis, and blood coagulation); pregnancy test; electrocardiogram; chest X-ray; vital signs (body temperature, pulse rate, and blood pressure); and body weight. All AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Definition of dose-limiting toxicity

Dose-limiting toxicity (DLT) was evaluated for 21 days after the first administration of siltuximab by the study evaluation team, which comprised all principal investigators and the sponsor's responsible medical officer. A DLT was defined as any nonhematologic toxicity of grade 3 or higher whose causal relationship to siltuximab could not be denied. Any toxicity thought to be controllable by supportive therapy (i.e., reversible to grade 1 or pretreatment grade within 3 days after any appropriate measure was taken) was not regarded as a DLT. Hematologic DLT included grade 4 neutropenia lasting more than 1 week, febrile neutropenia, and grade 4 thrombocytopenia lasting more than 1 week, or associated with hemorrhage. Thrombocytopenia with platelet transfusion, regardless of any grade, was also regarded as a DLT.

Siltuximab PK evaluation

During cycle 1, samples were collected predose and immediately, 4, and 6 h after administration on day 1 and on days 2, 4, 8, and 15. During cycles 2, 3, 4, and 5, samples were collected on day 1 before and immediately after siltuximab administration. During cycle 6, samples were collected on day 1 before administration. Serum concentrations of siltuximab were measured using a validated electro-chemiluminescence immunoassay method (lower limit of quantification: 0.045 μg/mL).

Noncompartmental analysis was conducted to calculate siltuximab PK parameters using Phoenix®WinNonlin® Version 6.2.1. (Pharsight Corp./Certara, St. Louis, MO, USA). In cycle 1, area under the serum concentration–time curve (AUC) from day 0 to 21 ($AUC_{0-21days}$) and AUC from 0 to infinity (AUC_{∞}) was calculated using the log-linear trapezoidal method. Terminal half-life ($t_{1/2}$) was determined using linear regression of log-transformed siltuximab concentration–time profile at the terminal phase of disposition. Maximum observed concentration (C_{max}), total systemic clearance (CL), and volume of distribution at terminal phase (Vd_z) were also calculated using standard noncompartmental analysis methods.

Immunogenicity evaluation

Serum samples for immunogenicity were collected predose on day 1 of cycle 1; at the time of discontinuation (end of treatment); and at 30 days, 8 weeks, and 12 weeks after the last administration of siltuximab. A validated and specific enzyme immunoassay method was used to detect anti-siltuximab antibodies in serum.

Assessment of efficacy

Antitumor response was assessed by the investigator based on findings obtained before the start of treatment and at the time of completion of an even number of cycles, or at the time of discontinuation, according to the European Group for Blood and Marrow transplantation (EBMT) criteria for assessment of multiple myeloma antitumor effect [19].

Statistical populations

Patients who received ≥1 dose of study drug were included in the safety population. The PK, immunogenicity, and efficacy population comprised all patients who received ≥1 administration of siltuximab and who had ≥1 appropriate postdose samples for serum concentration, immunogenicity, and efficacy evaluation, respectively.

Results

Patient demographics and characteristics

A total of 10 patients consented to participate in the study; nine patients were eligible and received ≥1 dose of siltuximab. Three patients received 5.5 mg/kg and the next six patients received 11.0 mg/kg of siltuximab (Fig. 1). All patients were Japanese with a median age of 66 years. Additional patient characteristics are summarized in Table 2. All patients had received one or two prior treatments for multiple myeloma, including proteasome inhibitors and immunomodulatory agents. No patients, however, received prior radiotherapy (Table 3).

Treatment compliance

Patients were 100 and >96 % compliant with siltuximab and all study treatments, respectively. The median exposure in days to siltuximab, bortezomib, and dexamethasone was 211 (range 22–549); 218 (range 29–556); and 219 (range 33–557), respectively.

Safety

There were no appreciable differences in the safety profiles between the two treatment groups for frequency (Table 4). There were no deaths during this study. Across all grades of severity, hematologic and gastrointestinal AEs were the most common, which all patients experienced. However, hematologic abnormalities were typically transient. The most common nonhematologic AEs across all grades included diarrhea and abnormal hepatic function (56 % each). One patient treated with 5.5 mg/kg of siltuximab experienced grade 3 pneumonia (confirmed to be caused due to *pseudomonas aeruginosa*) on day 22 of cycle 6, which was considered possibly related to siltuximab. After intravenous antibiotics, the pneumonia resolved, the patient's lung function improved, and clinical symptoms disappeared. Three patients treated with 11.0 mg/kg of siltuximab each had a serious AE (SAE): alveolitis allergic, interstitial lung disease, and colon cancer. The grade 1 interstitial lung disease abnormality occurred from

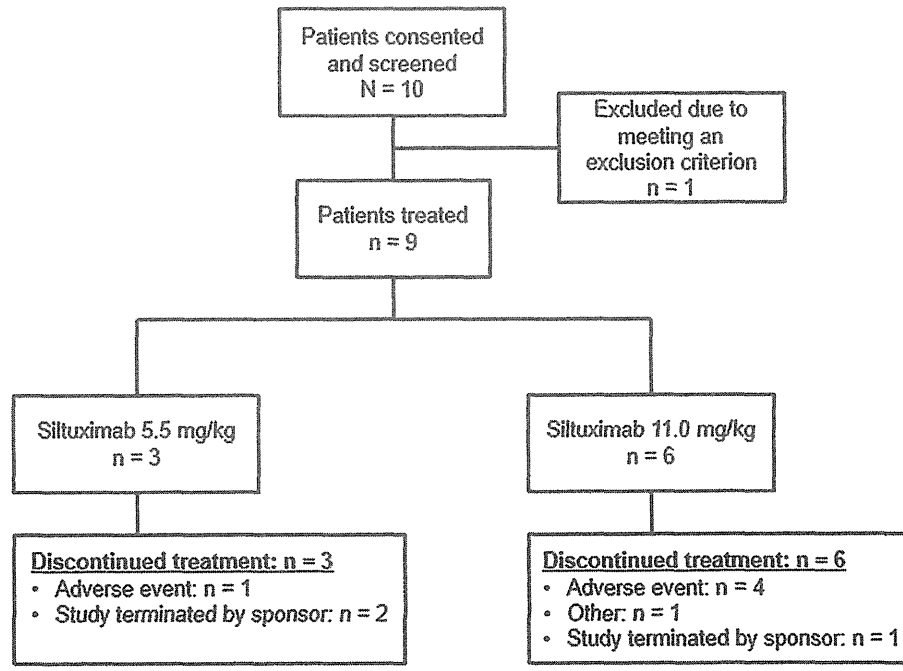

Fig. 1 CONSORT diagram

Table 2 Baseline characteristics and patient disposition

	Siltuximab 5.5 mg/kg ($n = 3$)	Siltuximab 11.0 mg/kg ($n = 6$)	All patients ($n = 9$)
Sex, *n* (%)			
Male	1 (33)	4 (67)	5 (56)
Female	2 (67)	2 (33)	4 (44)
Age (year)			
Mean ± SD	63.3 ± 8.1	65.8 ± 4.1	65.0 ± 5.3
Median (range)	67 (54, 69)	65 (61, 73)	66 (54, 73)
Type of myeloma, *n* (%)			
IgG	2 (67)	4 (67)	6 (67)
IgA	1 (33)	1 (17)	2 (22)
Bence Jones	0 (0)	1 (17)	1 (11)
Serum M-protein (g/dL)			
Mean ± SD	1.3 ± 0.1	2.3 ± 1.1	1.9 ± 1.0
Median (range)	1.3 (1.2, 1.3)	2.4 (0.5, 3.3)	1.8 (0.5, 3.3)
Duration since diagnosis (year)			
Mean ± SD	4.2 ± 2.7	1.9 ± 1.4	2.7 ± 2.1
Median (range)	4.8 (1.3, 6.6)	1.4 (0.2, 4.3)	1.5 (0.2, 6.6)
ECOG performance scale, *n* (%)			
0	3 (100)	3 (50)	6 (67)
1	0 (0)	3 (50)	3 (33)
β_2-microglobulin (mg/L)			
Mean ± SD	2.3 ± 0.4	3.8 ± 2.3	3.3 ± 2.0
Albumin, g/dL			
Mean ± SD	3.8 ± 0.2	3.7 ± 0.4	3.7 ± 0.3
KL-6, U/mL			
Mean ± SD	244.0 ± 102.3	207.8 ± 128.8	219.9 ± 115.4
ISS staging, *n* (%)			
I	3 (100)	2 (33)	5 (56)
II	0 (0)	2 (33)	2 (22)
III	0 (0)	2 (33)	2 (22)
Creatinine clearance (mL/min)			
Mean ± SD	75.5 ± 15.1	86.2 ± 30.7	82.6 ± 26.0

ECOG Eastern Cooperative Oncology Group, *Ig* immunoglobulin, *ISS* International Staging System, *KL-6* Krebs von den Lungen-6, *SD* standard deviation

Table 3 Prior multiple myeloma therapy

Prior therapy	Siltuximab 5.5 mg/kg ($n = 3$)	Siltuximab 11.0 mg/kg ($n = 6$)	All patients ($n = 9$)
Number of prior therapeutic MM regimens, *n* (%)			
1	2 (67)	3 (50)	5 (56)
2	1 (33)	3 (50)	4 (44)
Chemotherapy, *n* (%)			
Patients with any prior proteasome inhibitors	0 (0)	1 (17)	1 (11)
Patients with any prior immunomodulatory agents	0 (0)	1 (17)	1 (11)
Patients with any prior alkylating agents	3 (100)	4 (67)	7 (78)
Patients with any prior anthracyclines	2 (67)	4 (67)	6 (67)
Patients with any prior corticosteroids	3 (100)	6 (100)	9 (100)
Patients with any prior ASCT	1 (33)	1 (17)	2 (22)
Patients with any prior vinca alkaloid	2 (67)	4 (67)	6 (67)

ASCT autologous stem cell transplant, *MM* multiple myeloma

Table 4 Incidence and severity of adverse events of all grades (≥35 %) and grades 3/4 (≥35 %)

Adverse event	Siltuximab 5.5 mg/kg ($n = 3$)	Siltuximab 11.0 mg/kg ($n = 6$)	All patients ($n = 9$)
All adverse event			
All grades			
Hematologic			
Thrombocytopenia	3	6	9 (100)
Leukopenia	3	5	8 (89)
Lymphopenia	3	5	8 (89)
Neutropenia	2	5	7 (78)
Anemia	2	3	5 (56)
Leukocytosis	1	4	5 (56)
Neutrophilia	1	4	5 (56)
Nonhematologic			
Diarrhea	2	3	5 (56)
Hepatic function abnormal	2	3	5 (56)
Hyperlipidemia	1	3	4 (44)
Rash	1	3	4 (44)
Grades ≥3			
Hematologic			
Lymphopenia	3	5	8 (89)
Thrombocytopenia	1	3	4 (44)
Related to siltuximab*			
Hematologic			
Thrombocytopenia	3	6	9 (100)
Leukopenia	3	5	8 (89)
Lymphopenia	3	5	8 (89)
Neutropenia	2	5	7 (78)
Anemia	2	3	5 (56)
Nonhematologic			
Hepatic function abnormal	2	2	4 (44)

Data are presented as n or n (%)

*Adverse events whose relationship to siltuximab treatment was considered doubtful, possible, probably, or very likely

day 197 to the end of treatment. The investigator assessed the causal relationship between interstitial lung disease and bortezomib as probable, and between siltuximab and dexamethasone as possible. The alveolitis allergic event was considered grade 3 and probably related to siltuximab treatment. The alveolitis was treated with a prohibited concomitant drug (Solu-Cortef). Both events resolved, but led to treatment discontinuation. The colon cancer event was unrelated to the study drug and also led to treatment discontinuation. There were no infusion-related reactions. There was no DLT with either dose of siltuximab.

Pharmacokinetics and immunogenicity

Mean serum concentration–time profiles after administration of siltuximab 5.5 and 11.0 mg/kg during cycle 1 are shown in Fig. 2. The PK parameters of siltuximab are

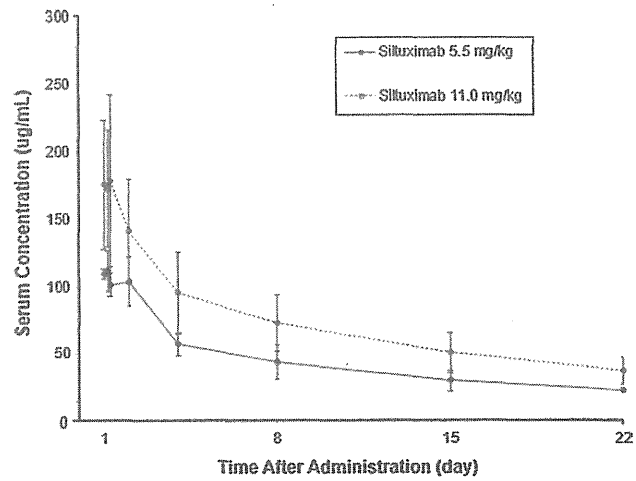

Fig. 2 Mean (± SD) serum concentration–time profiles of siltuximab by treatment in cycle 1

Table 5 Descriptive statistics for pharmacokinetic parameters of siltuximab by treatment

Parameter	Siltuximab 5.5 mg/kg ($n = 3$)	Siltuximab 11.0 mg/kg ($n = 6$)
C_{max} (μg/mL)	118.2 (8.78)	194.3 (52.46)
$AUC_{0-21days}$ (μg day/mL)	886.0 (197.75)	1,548.1 (324.14)†
AUC_{∞} (μg day/mL)	1347.0 (445.83)	2,273.9 (567.74)†
$t_{½}$ (day)	14.0 (2.73)	13.2 (3.86)†
CL (mL/day/kg)	4.406 (1.4922)	5.081 (1.2389)†
Vd_z (mL/kg)	84.90 (11.984)	94.29 (27.986)†

Data are presented as mean (standard deviation)

$AUC_{0\text{-}21\ days}$ area under the concentration time curve from time 0–21 days, AUC_{∞} area under the concentration time curve from time 0 to infinity, *CL* total systemic clearance of drug after intravenous administration, C_{max} maximum observed serum concentration, $t_{½}$ terminal half-life, Vd_z volume of distribution at terminal phase

† $n = 5$

summarized in Table 5. Following the first intravenous administration of siltuximab at both 5.5 and 11.0 mg/kg, the C_{max}, $AUC_{0-21days}$, and AUC_{∞} increased in an approximate dose-proportional manner. Mean $t_{1/2}$, CL, and Vd_z values were similar in the dose range of 5.5 and 11.0 mg/kg. Steady state of siltuximab could not be adequately assessed, as samples were not collected appropriately for some cycles. None of the nine patients with appropriate samples were positive for antibodies to siltuximab.

Efficacy

Regarding the antitumor effect using EBMT criteria, one (33 %) patient had CR while two (67 %) patients had partial response (PR) with 5.5 mg/kg. At a dose of 11.0 mg/kg, one (17 %) and two (33 %) patients had CR and PR, respectively. The remaining patients in the siltuximab 11.0 mg/kg group had no change [three (50 %)].

Discussion

Multiple myeloma remains an incurable disease, despite improvements in therapy in recent years [20]. Most patients experience relapses and develop refractory disease [4]. Due to resistance conferred by IL-6, proteasome inhibitors and corticosteroid treatments alone result in a poor response [11, 14, 21]. The addition of an IL-6 inhibitor to proteasome inhibitors and corticosteroid treatments has shown synergy in reduction of multiple myeloma cells in preclinical and clinical studies [22]. This study was conducted to evaluate the safety and tolerability as well as the PK, immunogenicity, and preliminary efficacy of siltuximab.

While all patients in this study had treatment-related AEs, no DLT was observed in either dose of siltuximab. The most common AEs were hematological and gastroenterological disorders. This finding is in line with the results of a phase 2 study conducted in the United States and The Netherlands, where patients with relapsed or refractory multiple myeloma received siltuximab 6 mg/kg (actual dose of 5.5 mg/kg, based upon drug product vial) on days 1 and 15 of 28-day cycles with or without dexamethasone. Hematological AEs were of less severity in the phase 2 study [4]. Infections in the current study did not seem to be dose dependent, as there were more infection-related events in the treatment group receiving the lower dose of siltuximab. In the phase 2 study, infections including upper respiratory infection, cellulitis, and pneumonia occurred in 57 % of dexamethasone combination-treated patients, and 18 % of patients experienced ≥3 grade infections [4]. Results from another phase 2 study in patients with multiple myeloma treated with bortezomib plus either placebo or siltuximab demonstrated only a difference of 17 % in grade 3 and higher infections between the two treatment arms [23]. However, preclinical investigation showed minor and/or transient reductions in lymphocyte activities after treatment of cynomolgus monkeys with siltuximab (unpublished observations). IL-6 has an important role in immune response, and inhibition of IL-6 may further increase the risk of infection in patients immunocompromised by advanced multiple myeloma plus treatment with bortezomib or dexamethasone. Therefore, careful surveillance of infection-related toxicity during siltuximab-based therapy is warranted.

The PK parameters were similar to an earlier phase 1 study conducted in the United States in which patients received siltuximab 12 mg/kg (actual dose of 11 mg/kg, based upon drug product vial) every 3 weeks by 1-hour intravenous infusion [10]. Regarding immunogenicity, similar to the preceding phase 1 study [10], no antibodies to siltuximab were detected in any of the nine patient samples in this study.

Preliminary efficacy data were available as six of the nine patients, across both doses, had CR or PR (22 and

44 %, respectively) with the combination treatment. In the earlier phase 1 study, two of the 13 evaluable patients (17 %) with multiple myeloma achieved CR with siltuximab as a single agent [10]. A phase 2 study in which patients received siltuximab alone or in combination with dexamethasone did not produce any CRs; however, 8/47 patients had PR (17 %) [4]. The phase 2 study in patients with siltuximab plus bortezomib and bortezomib alone demonstrated an overall response rate of 55 (CR 11 %) and 47 % (CR 7 %), respectively [23]. Despite the numerically higher response rate, combination treatment did not lead to a statistically significant improvement in progression-free survival. However, siltuximab has been shown to provide long-lasting clinical activity [10] and durable tumor and symptomatic response in multicentric Castleman's disease, where IL-6 is also an important component of pathogenesis [24], at 11 mg/kg (34 % of patients had CR or PR) [9].

From our study we confirmed the tolerability of siltuximab up to 11.0 mg/kg in combination with bortezomib and dexamethasone as well as preliminary efficacy in Japanese patients with relapsed/refractory multiple myeloma. Based on the results, we established a recommended dose of 11 mg/kg of siltuximab in combination with bortezomib and dexamethasone. This is consistent with the global single-agent recommended dose of siltuximab in multicentric Castleman's disease [9]. Siltuximab is being further investigated in earlier myeloma settings, such as smoldering myeloma, as well as in other indications including multicentric Castleman's disease.

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Conflict of interest Janssen Pharmaceutical K.K. supported this study and supplied the investigational drugs. K. Suzuki, T. Suzuki, K. Anso, D. Maruyama, M. Kojima, M. Ogura, J. Kuroda, and Y. Abe have no conflicts of interest to disclose. M. Taniwaki has received grants from Janssen Pharma, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd., Celgene, and Kyowa Hakko Krin Co., Ltd. M. Achira and K. Iizuka are employees of Janssen Pharmaceutical K.K., Tokyo, Japan. H. Otani was an employee of Janssen Pharmaceutical K.K.M. Ogura was at Nagoya Daini Red Cross Hospital during the study conduct, and is now affiliated with Fujita Health University and Tohoku University as well as Nagoya Daini Red Cross Hospital. K. Iizuka was at Janssen Pharmaceutical K.K. during the study conduct, and is now affiliated with Janssen Diagnostics Inc., Raritan, NJ, USA.

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V. 特　　論

二次発がん

蒔田真一　丸山　大

Second primary malignancies after the treatment of multiple myeloma

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Abstract

Outcome of the patients with multiple myeloma has improved significantly in the last decade, mainly because of the introduction of new agents such as thalidomide, bortezomib and lenalidomide. Improvements in survival among patients with multiple myeloma suggest that the incidence of second primary malignancies (SPMs) may increase in the future. Many factors could affect increasing the risk of SPMs, such as treatment factors, myeloma related factors, host genetic factors, and so on. Especially, previous clinical trials suggested that extended exposure to the melphalan and lenalidomide containing regimens are the important risk factors of SPMs. Although numbers of SPMs are small, for individual patients who develop SPMs, the outcomes are devastating. Therefore, we need to discuss not only the efficacy but also the risks of SPMs associated with the treatment in the patients with multiple myeloma in new agents era.

Key words: second primary malignancies, multiple myeloma, lenalidomide

はじめに

多発性骨髄腫(multiple myeloma: MM)は依然として難治性疾患ではあるが，新規薬剤の登場により近年その予後が改善している．このため，長期生存者における二次発がん(second primary malignancies: SPMs)は現在の骨髄腫診療における重大な問題点の一つとなっている．MM患者におけるSPMsの発症率は10％程度と報告されており[1](**図1**)，MMに対する治療歴のみならず，MM患者を取り巻く様々な要因を背景として発症する[2](**図2**)．

1. 治療に伴う要因

1) アルキル化剤

アルキル化剤はMM診療におけるkey agentsの一つである．経口アルキル化剤による治療後に発症するSPMs(特にacute myeloid leukemia: AML)についてはこれまでも複数の報告がある(**表1**)．Bergsagelら[3]が行った前方視的研究では，メルファラン(melphalan: MEL)，シクロホスファミド(cyclophosphamide: CPA)およびカルムスチン(carmustine)という3つのアルキル化剤を含む治療レジメンによる二次性AMLの発症リスクが副次的に検討された．治療を受け

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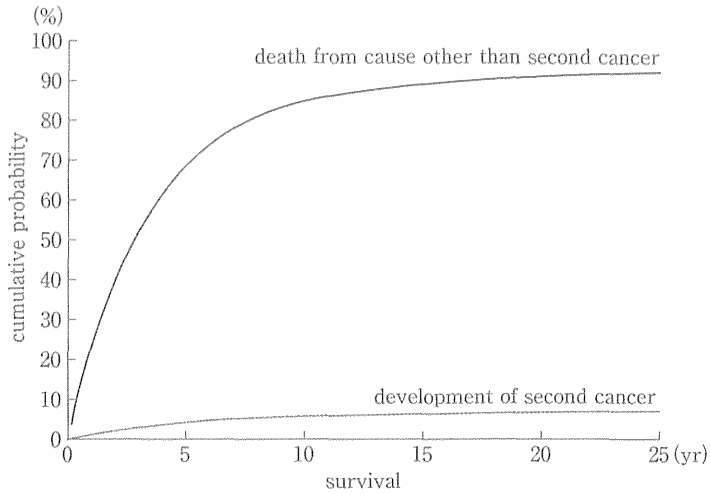

図1　二次がんの発症率とその他の原因による死亡率の比較(文献[1]より引用)
Surveillance, Epidemiology, and End Results Program of the National Cancer Institute(NCI-SEER)のデータベースを用いて1973-2008年に米国で診断されたMM患者33,229人を対象に，SPMsの発症率とその他の原因による死亡率に関して解析したものである．MMはいまだ治癒が難しい疾患であり，原病による死亡率は高い．一方でSPMsの発症頻度は10％程度であるが，一度発症すれば難治である．

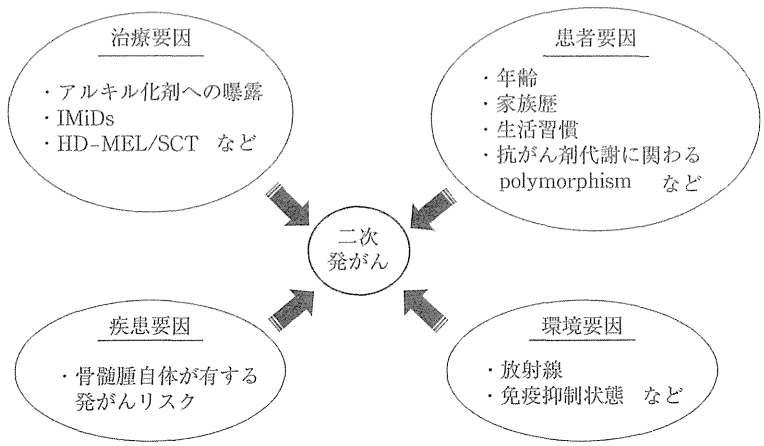

図2　二次発がんの危険因子(文献[2]より改変)
MM患者における二次発がんには，治療要因のみならず，患者要因，環境要因など様々な背景因子が関与している．

た364人中，14人でAMLの発症を認め，治療から50カ月の時点におけるAMLの発症リスクは17.4％に上ることが示された．

アルキル化剤の中でもMELの方がCPAより二次性AMLのリスクが高い可能性を示唆する報告がある[4]．またMELによる二次性AMLの発症リスクに関しては，Cuzick[5]らにより累積投与量との関連性が示唆されている．

1980年代にhigh dose MEL療法に引き続く自家造血幹細胞移植(HD-MEL/ASCT)が導入され，それに伴うSPMsのリスクが検証されるようになった．

Govindarajanら[6]はHD-MEL/ASCTへの導入化学療法として，アルキル化剤の曝露量が異な

表1 二次発がんに関する報告

著者	試験デザイン/試験期間	患者数	二次がんの発症率(%)	血液腫瘍を発症した患者数(%)	固形癌を発症した患者数(%)
randomized phase III trials					
Attal, et al[8]	Len vs PL after HD-MEL/ASCT	608	8.5 vs 3.6	13/306(4.2%) vs 5/302(1.7%)	15/306(5%) vs 7/302(2%)
McCarthy, et al[9]	Len vs PL after HD-MEL/ASCT	460	7.8 vs 2.6	8/231(3.5%) vs 1/229(0.4%)	10/231(4.3%) vs 5/229(2.2%)
Palumbo, et al[10]	MPL-L vs MPL vs MP	455	8 vs 6 vs 3	7/150(5%) vs 5/152(3.3%) vs 1/153(0.7%)	5/150(3.3%) vs 4/152(2.6%) vs 3/153(2%)
prospective studies					
Govindarajan, et al[6]	NR	188	3.8	3.8	NR
Bergsagel, et al[3]	1973-1977	364	3.8	3.8	NR
retrospective studies					
Cuzick, et al[5]	1964-1975	648	1.9	1.9	NR
Finnish Leukaemia Group[13]	1979-1985	432	9.2	3.9	5.3
Mailankody, et al[7]	1986-2005	8,740	6.6	0.8	5.8
Przepiorka, et al[14]	1996-2005	82	12.2	12.2	NR
Barlogie, et al[15]	1989-2007	2,418	1.1	1.1	NR
Hasskarl, et al[16]	1997-2008	589	3	1	2
Usmani, et al[17]	1998-2009	1,148	6.4	3.1	3.2

Len: lenalidomide; PL: placebo; HD-MEL/ASCT: high dose melphalan with autologous stem cell transplantation; MPL-L: melphalan, prednisone, lenalidomide and lenalidomide maintenance; MPL: melphalan, prednisone, lenalidomide; MP: melphalan, prednisone; NR: not reported.

る2群を比較する試験を行った．この試験のGroup 1では，アルキル化剤を含まない導入化学療法に引き続き，HD-MEL/ASCTが実施された．Group 2では，当時の標準的治療として複数サイクルのアルキル化剤を含む化学療法が実施された後にHD-MEL/ASCTが行われた．いずれのGroupでもhigh dose CPA療法(HD-CPA)の回復期に末梢血幹細胞が採取され，引き続いてHD-MEL/ASCTが2回行われた．観察期間中央値はGroup 1で36カ月，Group 2で29カ月であり，Group 1では骨髄異形成症候群(myelodysplastic syndrome: MDS)の発症は認められなかったが，Group 2では7人にMDSの発症が認められた．この試験から，彼らはHD-MEL/ASCTそのものより，導入化学療法で使用されるアルキル化剤の累積投与量の方が治療関連MDSの発症により影響していると結論づけている．更に，Swedenで行われた8,740人のMM患者に関するpopulation based study (1986-2005)ではHD-MEL/ASCTが導入される前後で治療関連MDS/AMLの割合が増えていないことが報告された[7]．これらの結果から，HD-MEL/ASCTを含む治療戦略は，通常量のアルキル化剤のみによる治療と比して，治療関連MDSや二次性AMLのリスクを増加させない可能性が示唆されている．

2) 未治療MM患者における lenalidomideとSPMs

未治療MM患者を対象としたlenalidomide併用導入療法およびlenalidomide維持療法におけるSPMsに関してはIFM 2005-02[8]，CALGB 100104[9]およびMM-015[10]という3つのrandomized phase III trialによる報告がある．IFM 2005-02とCALGB 100104はHD-MEL/ASCT後のlenalidomide維持療法の有用性を検証した試験であり，両者ともprogression free survivalをprimary endpointとして，lenalidomide 10-15 mg/dayをASCTの3-6カ月後から内服する

群とplacebo群とを比較する設定で行われた．ただし，CALGB 100104試験のplacebo群では疾患増悪後に80％の患者がlenalidomide維持療法群にcross overしている．IFM 2005-02とCALGB 100104におけるlenalidomide投与群でのSPMsの頻度は各々5.5％と6.5％だったのに対して，placebo群では1％と2.5％だった．

MM-015では移植非適応未治療MM患者を対象に，lenalidomide併用のMEL+prednisone(MPL)療法を行った後，疾患増悪までlenalidomideによる維持療法を行うMPL-L群と，MPL+placebo群そしてMP群の3群が比較された．SPMsは，MPL-L群で9人(2.70％)，MPL群で7人(2.05％)，MP群で4人(1.20％)であった．

これらの結果から，少なくともMELやASCTを施行する設定とともにlenalidomideを長期使用する際にはSPMsに留意しなければならないことは確かであろう．またPalumbo[11]らにより，未治療MM患者に対してlenalidomide併用の有無によるSPMsの発症リスクに関するmeta-analysisが行われた．Lenalidomide併用レジメンにおけるSPMsの5年累積発症率は6.9％であったのに対してlenalidomideを併用しないレジメンでは3.8％であった．興味深いことに，lenalidomideとMELとの併用療法で治療された患者はSPMsのリスクが高かった．今後，lenalidomideと他剤との併用に際して，特に若年患者においてはMELに代わってCPAや，あるいはアルキル化剤以外の抗がん剤が選択されていく可能性がある．

LenalidomideによりSPMsのリスクが高くなる機序は明らかではない．最近cereblonというタンパクをlenalidomideが阻害していることが明らかになった．cereblonはE3 ubiquitin ligase complexを形成するタンパクの一つである．E3 ubiquitin ligase complexにはDDB1というDNA修復に関わるタンパクも含まれており，lenalidomideがcereblonを阻害することでDDB1の機能が低下しDNA修復機構が障害されるのではないかという仮説が提唱されている[12]．

2. 原病による要因

MMは分子生物学的には多彩な性質をもつheterogenousな疾患群である．また腫瘍が進行していく過程でepigeneticな変化や細胞内シグナル伝達系の変化が起こることが知られている．このような分子生物学的特徴がMDS/AMLへの進展に関与している可能性がある．

Swedenから報告されたpopulation-based study[9]によりmonoclonal gammopathy of undetermined significance(MGUS)患者においてMDS/AMLのリスクが一般集団の8倍も高いことが示された．MGUSは原則として無治療経過観察される疾患群であり，化学療法などの影響では説明できず，疾患自体がSPMsのリスクを有している可能性が考えられている．

3. その他の要因

化学療法のみならず，放射線治療や環境要因(塩素系溶剤)，行動要因(喫煙，飲酒，肥満)，遺伝子多型などの宿主要因もSPMsの発症に寄与しているといわれている[2]．しかし，これらの非治療関連因子に関しては十分な検討がなされていないのが現状である．

おわりに

近年の新薬の臨床導入により，多発性骨髄腫の予後は改善を認めているが，SPMsをはじめとした，晩期毒性の発症に留意すべきである．またこれらのリスクを患者へ説明することを心がけなければならない．

文　献

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