

Phase I study of LY2181308, an antisense oligonucleotide against survivin, in patients with advanced solid tumors

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Abstract

Purpose LY2181308 is an antisense oligonucleotide that complementarily binds to survivin mRNA and inhibits its expression in tumor tissue. This phase I dose escalation study evaluated the tolerability, pharmacokinetics, and anticancer activity of LY2181308 in Japanese.

Methods Patients with solid tumors refractory to standard therapy received LY2181308 (400, 600, or 750 mg) as a 3-h intravenous infusion for 3 consecutive days and thereafter once a week.

Results LY2181308 was administered to 14 patients, aged 44–73 (median 60) years. Flu-like syndrome, prolonged prothrombin time-international normalized ratio (PT-INR), thrombocytopenia, and fatigue were common reversible grade 1/2 toxicities. The dose-limiting toxicity was reversible grade 3 elevation of ALT/AST/ γ -GTP in 1 patient treated at the 750-mg dose. Pharmacokinetic analysis showed a long terminal half-life of 21 days and an extensive tissue distribution of LY2181308. In 12 evaluable patients, one patient had stable disease, while the remaining 11 patients had progressive disease.

Conclusions LY2181308 monotherapy is well tolerated up to 750 mg with a manageable toxicity, the pharmacokinetic profile warrants further evaluation of LY2181308 in combination with cytotoxic agents or radiotherapy.

Keywords Antisense oligonucleotide · Pharmacokinetics · Phase I · Survivin

Introduction

Survivin, a member of the inhibitor of apoptosis family of proteins (IAP), regulates apoptosis and promotes cell proliferation [1]. Survivin is highly expressed during fetal development and rarely detectable in normal adult tissues [1]. However, overexpression of survivin has been reported in the vast majority of solid tumors and leukemias [2, 3].

LY2181308 is a novel second-generation antisense oligonucleotide (ASO) designed to complementarily bind to human survivin mRNA, inhibit the gene/protein expression, and consequently restore the normal apoptotic pathway in cancer cells. The antitumor activity of LY2181308 is correlated with inhibition of survivin [4, 5]. Furthermore, LY2181308 potentially inhibited the expression of survivin mRNA and protein in human tumor cell lines [6]. These results justified its evaluation in clinical studies. Recently, a first-in-human dose study established the tolerability of LY2181308 at 750 mg [7]. ASOs are known to accumulate in the liver, where they can cause off-target hepatic toxicities [8].

In Japanese patients, genetic variations that influence metabolism and safety of anticancer drugs, such as UDP-glucuronosyltransferase (UGT) 1A1 and multidrug resistance protein (MRP) 1, have been identified [9]. Also, there are genetic variations that can predispose Japanese patients

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to an altered response to inflammation as highlighted by polymorphisms of the TNF gene [10]. Because ASO administration is associated with complement activation leading to subsequent inflammatory reactions, including TNF release [11], Japanese patients may be more susceptible to ASO administration and its associated off-target inflammation. Hence, the objective of this study is to determine the tolerability, pharmacokinetics, and anticancer activity of LY2181308 in Japanese patients with advanced solid tumors.

Materials and methods

Patient eligibility

Patients with malignant solid tumors were eligible after failing standard therapies or if there was no approved treatment available. Eligibility criteria included: age 20–75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1; adequate bone marrow, hepatic, renal, and coagulative function (absolute neutrophil count $\geq 1,500/\mu\text{l}$, platelet count $\geq 100,000/\mu\text{l}$, hemoglobin level 9.0 g/dl , total bilirubin $\leq$ upper limit of normal range [ULN], aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≤ 2.5 times ULN, estimated creatinine clearance $\geq 50\text{ ml/min}$, normal prothrombin time-international normalized ratio [PT-INR, 0.8–1.2], and normal activated partial thromboplastin time [APTT, 23–40 s]); discontinuation of prior anticancer therapy 28 days before enrollment to this study or conclusion of palliative radiotherapy 14 days prior to starting on study; written informed consent. Exclusion criteria included the following: diagnosed pregnancy or ongoing lactation; symptomatic brain metastasis; active hepatitis B, C, or human immunodeficiency virus (HIV); and concomitant use of any anticoagulant drugs. The protocol was approved by the Institutional Review Board. The study was consistent with Good Clinical Practice and all applicable laws and regulations in Japan.

Drug administration and dose escalation procedure

LY2181308 (Eli Lilly and Company, IN, USA) was administered via intravenous infusion over 3 h on day 1–3 of the initial cycle (cycle 1 [day 1–7]) as a loading dose and then once a week as maintenance dose (cycle 2 [day 8–28] and onwards [28 days/cycle]). The content of each vial containing 100 mg in 4 ml of buffer was added to 500 ml of saline. The starting dose was 400 mg, with subsequent dose escalations to 600 and 750 mg in a classical 3 + 3 design. Dose-limiting toxicities (DLTs) were evaluated at each dose level (400:600:750 mg = 3:3:6 patients).

The maximum tolerated dose (MTD) was defined as the highest dose level at which no or one patient experienced a DLT.

DLT was defined as any event that met at least one of the following criteria: (1) febrile neutropenia or grade 4 neutropenia persisting more than 4 days; (2) grade 4 decreased hemoglobin or thrombocytopenia, or thrombocytopenia requiring blood transfusion; (3) grade 3 APTT prolongation observed at the end of the study drug administration and persisting $\geq 48\text{ h}$ after administration; (4) non-hematological toxicities of grade 3 or higher (nausea, vomiting, anorexia, fatigue, constipation, diarrhea, and abnormal electrolytes were not considered DLTs if controllable with appropriate treatment); (5) discontinuation/postponement of study drug administration due to a toxicity other than those mentioned above and the total amount of administered study drug $< 80\%$ of the total amount scheduled for the first 28 days; and (6) other toxicities that were judged as DLTs by the investigator.

Treatment assessment

Tolerability was evaluated in all patients for toxicities, clinical laboratory tests, coagulants, and vital signs. Toxicities were graded according to the Common Terminology Criteria for Adverse Events version 3.0 [12].

Tumor responses were assessed in patients who had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.0 [13].

Pharmacokinetics

Pharmacokinetic evaluation was performed in all patients during cycles 1 and 2. The concentration of LY2181308 in plasma was measured by enzyme-linked immunosorbent assay (ELISA) using antidigoxigenin-AP (Roche) to capture LY2181308. The minimum quantifiable concentration was 1.875 ng/ml in plasma. Non-compartmental pharmacokinetic parameters were calculated. Population pharmacokinetic analysis was also conducted in a model-dependent manner using a NON-linear Mixed Effect Model (NONMEM) program version VI.

Results

Patient characteristics

Fourteen patients in this study had the typical characteristics in a phase I study (Table 1). The most common histology was lung cancer (six patients), followed by pancreatic cancer (four patients). Approximately, half of the patients had more than four prior chemotherapies. A total of 31

Table 1 Patient characteristics

Variable	400 mg (n = 4)	600 mg (n = 4)	750 mg (n = 6)	Total (n = 14)
Sex				
Male	3	4	4	11
Female	1	0	2	3
Age, years				
Median	58.5	63.5	59.0	60.0
Range	44–73	60–69	49–66	44–73
Primary tumor type				
Lung	1	1	4	6
Pancreas	2	2	0	4
Intrahepatic cholangiocarcinoma	0	1	0	1
Uterus	1	0	0	1
Esophagus	0	0	1	1
Breast	0	0	1	1
ECOG PS				
0	1	1	6	8
1	3	3	0	6
Prior therapy				
Cancer-related surgery	3	1	4	8
Radiotherapy	0	1	5	6
Chemotherapy	4	4	6	14
≥4 prior chemotherapy regimens	1	2	3	6

ECOG PS eastern cooperative
oncology group performance
status

cycles were administered; the median number of cycles administered per patient was 2 (range 1–4). The maximum treatment period was 93 days.

Safety and tolerability

DLT was evaluated in 12 of the 14 patients. At the 750-mg dose, one patient with small cell lung cancer and a PS of 0 experienced DLTs of grade 3 elevation including AST, ALT, and γ -GTP on day 8. These events were asymptomatic and resolved without medication. Another patient at the 600-mg dose experienced a grade 3 total bilirubin elevation, which was not considered a DLT but rather a result of tumor progression. Hence, the MTD was established at the 750-mg dose level.

In addition to these toxicities, we observed flu-like symptoms (fever, chills, and hyperhidrosis), prolonged PT-INR, thrombocytopenia, and fatigue as grades 1/2 (Table 2). Almost all flu-like symptoms were observed during the loading dose of day 1–3. They were manageable with oral antipyretic such as acetaminophen. Prolonged PT-INR and thrombocytopenia were also grade 1/2, and there was no medical treatment required such as blood transfusions. Grade 1 fatigue occurred in eight patients. Grade 3 lymphocytopenia and anemia were only observed

in one patient treated at the 400-mg dose; they were not considered drug related. Concentrations of complement fragments Bb and C3a were elevated on day 3 and returned to baseline after day 8 (Fig. 1).

Anticancer activity

Twelve of the fourteen patients met RECIST guideline for antitumor response assessment. At the 600-mg dose, 1 patient with intrahepatic cholangiocarcinoma had stable disease, but the remaining 11 patients had progressive disease.

Pharmacokinetics

Pharmacokinetic analysis was performed in all 14 patients (Fig. 2). The interindividual coefficient of variation (CV%) of AUC for LY2181308 was moderate. Pharmacokinetic parameters on day 3 were similar to those on day 1, suggesting no accumulation of study drug in plasma. The multiphasic disposition pharmacokinetic profile of LY2181308 was adequately described by a 4-compartment model with elimination from the peripheral compartment. The mean terminal $t_{1/2}$, distribution clearance (CL), elimination CL, and V_{ss} estimated by the model were 21 days, 2.0 l/h,

Table 2 Drug-related toxicities at selected dose levels

Grade	400 mg (n = 4)		600 mg (n = 4)		750 mg (n = 6)		All (n = 14)			
	1–2	≥3	1–2	≥3	1–2	≥3	1	2	≥3	All
Hematological toxicities										
Decreased platelet count	3	0	3	0	4	0	7	3	0	10
Decreased lymphocyte count	0	1	1	0	2	0	2	1	1	4
Decreased Hb	0	1	2	0	0	0	1	1	1	3
Decreased WBC	0	0	1	0	2	0	3	0	0	3
Non-hematological toxicities										
Increased PT-INR	3	0	3	0	5	0	11	0	0	11
Hyperhidrosis	2	0	3	0	6	0	11	0	0	11
Pyrexia	2	0	3	0	6	0	8	3	0	11
Fatigue	3	0	1	0	4	0	8	0	0	8
Increased CRP	2	0	4	0	2	0	8	0	0	8
Prolonged prothrombin time	1	0	1	0	5	0	7	0	0	7
Increased β -2 microglobulin urine	1	0	4	0	2	0	7	0	0	7
Anorexia	2	0	0	0	3	0	4	1	0	5
Chills	1	0	1	0	3	0	5	0	0	5
Diarrhea	2	0	1	0	2	0	5	0	0	5
Increased ALT	1	0	1	0	2	1 ^a	3	1	1	5
Decreased blood albumin	2	0	0	0	2	0	4	0	0	4
Headache	1	0	0	0	3	0	4	0	0	4
Injection site pain	2	0	1	0	1	0	4	0	0	4
Nausea	0	0	1	0	3	0	3	1	0	4
Prolonged APTT	1	0	0	0	3	0	4	0	0	4
Increased AST	1	0	1	0	1	1 ^a	3	0	1	4
Flushing	1	0	1	0	1	0	3	0	0	3
Hypothermia	1	0	0	0	2	0	0	3	0	3
Increased ALP	0	0	0	0	3	0	2	1	0	3
Increased blood triglycerides	0	0	0	0	3	0	2	1	0	3
Increased γ -GTP	0	0	0	0	1	2 ^a	1	0	2	3

ALP alkaline phosphatase, ALT alanine aminotransferase, APTT activated partial thromboplastin time, AST aspartate aminotransferase, CRP c-reactive protein, γ -GTP gamma-glutamyl transpeptidase, Hb hemoglobin, PT-INR prothrombin time-international normalized ratio

^a Grade 3 elevations in AST/ALT/ γ -GTP in one patient were judged as DLTs

28.1 l/h, and 2.05×10^5 l, respectively. Model analysis showed that 84.5% of plasma LY2181308 was distributed to tissue within 8 h after the initiation of administration.

Discussion

Survivin is attracting considerable interest as a potential target for cancer therapy because it is upregulated in most malignancies and may play a role in blocking apoptosis in cancer cells [14]. LY2181308 is the first ASO to successfully inhibit survivin. Overall, LY2181308 was generally well tolerated in patients with advanced solid tumors. MTD was reached at 750 mg, and the 750-mg dose was recom-

mended for further investigations. This study revealed a potential mild hepatotoxicity at the 750-mg dose in contrast to the first-in-human dose study in which this event was only observed at doses of 900 and 1,000 mg [7]. Other clinically important toxicities included flu-like symptoms, elevated PT-INR, thrombocytopenia, and fatigue. The frequency of flu-like symptoms, such as fever, was higher (79%) than that of previous study (32%) [7]. Despite these two main differences, LY2181308 had similar tolerability profile in Japanese as in Caucasian or other races [7]. However, the low-grade toxicity, the reversibility profile, and the medical treatment with antipyretics suggest that these differences between two studies may be marginal or insignificant.

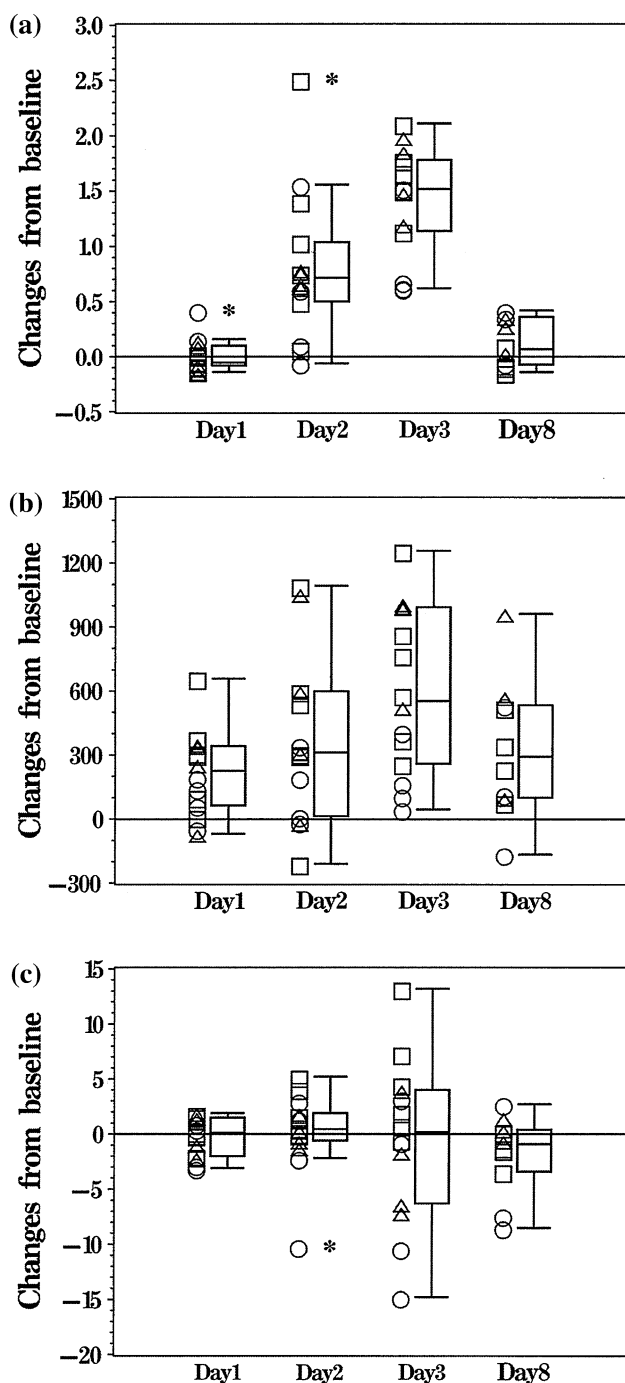


Fig. 1 Change in plasma concentration of complement fragments. Change in plasma concentration of complement fragments from baseline (before administration) to 15 min after the completion of infusion (**a**, Bb; **b** C3a; **c**, C5a). Symbols = circles 400 mg/time; triangles 600 mg/time; squares 750 mg/time. Normal range = Bb, 0.35–0.85 μ g/ml; C3a, 305–1,239 ng/ml; C5a, 13.5–58.7 ng/ml

One reason for the induction of flu-like symptoms would be the off-target activation of complement after infusion of ASOs. Increase in levels of complement fragments C3a and Bb on day 3 was comparable to those found in preclinical

studies using monkeys [15] and past phase I studies of other ASOs [16]. These complement elevations were acceptable since there was no signs of abnormal immune responses including anaphylaxis. Also, increases in C-reactive protein were equally distributed across all three dose groups, thus suggesting that the complement activation was similar in all patients.

Thrombocytopenia and decreased hemoglobin were observed as grade 1/2. In just one case, grade 3 was observed, but hematologic toxicities were generally mild. The ASO effect on reducing platelet counts may have two potential mechanisms: one is related to the well-known off-target effect of ASOs [8] and the other to the inhibition of survivin. For instance, survivin-depleted mice have reduced hemoglobin, white blood cell, and platelet counts as a result of loss in hematopoietic progenitor cells [17]. Lastly, it should be noted that despite the high accumulation of ASOs in the kidney, no elevation or signs and symptoms related to kidney dysfunction were observed.

The pharmacokinetic profile had a long half-life of 21 days. Consistent with the long terminal $t_{1/2}$, the CL to tissue and elimination CL were low to moderate, and the V_{ss} was large. It is thought that the long terminal $t_{1/2}$ represents plasma-tissue concentration during the tissue elimination phase of LY2181308 once the distribution equilibrium between plasma and tissues has been reached [8]. These results were comparable to the pharmacokinetic results from LY2181308 studies in mice and monkeys, showing that rapid tissue distribution (within 24 h) cleared approximately 90% of the drug from plasma. The linearity of LY2181308 was not evaluated in this study due to the small number of patients.

Finally, 12 patients met the RECIST guideline for tumor response assessment. Only one patient had stable disease, while the others had progressive disease. While these data do not suggest any single-agent activity of LY2181308, it should be stressed that this was also not expected. LY2181308 is expected to have activity in conjunction with apoptosis-inducing agents, such as chemotherapy or radiation, and render previously apoptosis-resistant cells sensitive to pro-apoptotic treatments. For instance, paclitaxel or docetaxel resistance has been associated with increased survivin expression [18–20]. Besides, radiotherapy treatment is enhanced after blocking survivin expression in colorectal cancer models [21]. Based on these observations and the favorable toxicity profile of LY2181308, three phase 2 studies are being/have been conducted in conjunction with cytotoxic drugs: (1) combination with cytarabine and idarubicin for acute myeloid leukemia (completed), (2) combination with docetaxel and prednisone for prostate cancer (on-going), and (3) combination with docetaxel for non-small cell lung cancer (ongoing).

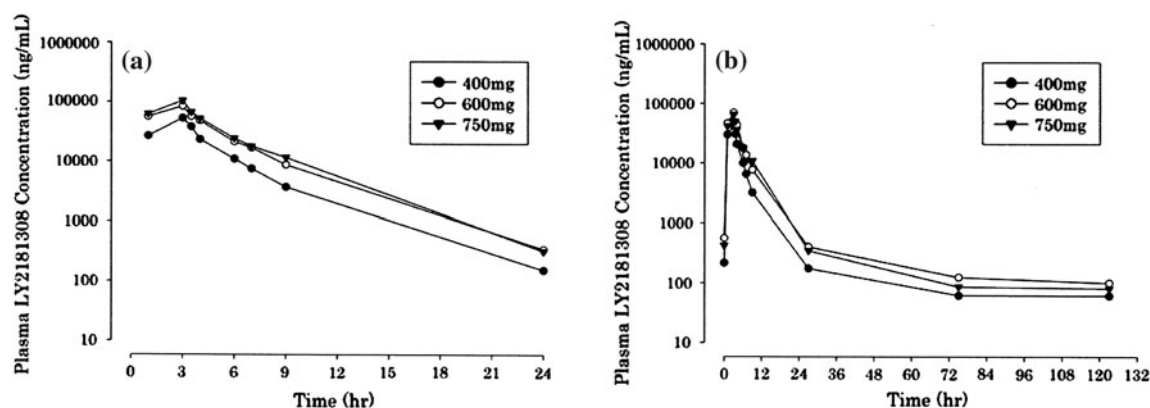


Fig. 2 Mean plasma concentration–time profiles of LY2181308. Mean plasma concentration–time profiles of LY2181308 on day 1 (a) and day 3–7 (b). C_{max} and AUC at 750 mg were comparable between Japanese and non-Japanese patients [21]

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Conflict of interest Results from this study were presented in part at the 21st (2009) Molecular Targets and Cancer Therapeutics Conference (EORTC-NCI-AACR Symposium; Boston, 15–19 November) [22]. T. Tamura serves as a consultant to Eli Lilly Japan K.K. T. Fujimoto, R. Sekiguchi and K. Uenaka are full-time employees of Eli Lilly Japan K.K. S. Callies is a full-time employee of Eli Lilly and Company. M. Tanioka, H. Nokihara, N. Yamamoto, Y. Yamada, K. Yamada and Y. Goto have no conflicts of interest to disclose.

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