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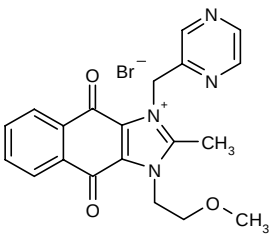
YM-155

Apoptosis Inducer
Survivin Expression Inhibitor
Oncolytic

3-(2-Methoxyethyl)-2-methyl-4,9-dioxo-1-(pyrazin-2-ylmethyl)-4,9-dihydro-3*H*-naphtho[2,3-*d*]imidazol-1-ium bromide

InChI=1/C20H19N4O3.BrH/c1-13-23(9-10-27-2)17-18(24(13)12-14-11-21-7-8-22-14)20(26)16-6-4-3-5-15(16)19(17)25;/h3-8,11H,9-10,12H2,1-2H3;1H/q+1;/p-1



$C_{20}H_{19}BrN_4O_3$
Mol wt: 445.3099

CAS: 781661-94-7

CAS: 753440-91-4 (free base)

EN: 413279

Abstract

YM-155, a small-molecule survivin suppressant, has demonstrated potent antiproliferative activity against a wide spectrum of human tumor cell lines. Preclinical studies indicated that the antitumor activity of YM-155 in various human tumor xenograft models, including prostate cancer, lung cancer and melanoma, was more potent compared to available anticancer agents (equipotent to paclitaxel) without causing loss of body weight or hematological toxicity. Three-day continuous infusion of YM-155 completely inhibited tumor growth and induced marked tumor regression in mice bearing human prostate tumor xenografts. Continuous infusion of YM-155 was associated with greater efficacy and less toxicity than bolus injection. YM-155 as monotherapy demonstrated promising anticancer activity and an acceptable toxicity profile in patients with various types of cancer and is currently undergoing phase II clinical trials.

Synthesis

YM-155 can be synthesized as follows:

3-Chloro-2-[*N*-(2-methoxyethyl)acetamido]naphthoquinone (I) is condensed with 2-(aminomethyl)pyrazine (II) in benzene to afford the diaminonaphthoquinone derivative (III) (1), which is cyclized to the title naphthoimidazolium bromide by treatment with HBr in hot EtOH or MeOH (1, 2). Scheme 1.

Background

Survivin, a key member of the inhibitor of apoptosis (IAP) family, is overexpressed in many human tumors but not in normal tissues, and its overexpression in tumors is associated with a poor prognosis and shorter survival times (3, 4). By using a cell-based high-throughput screening and lead optimization, scientists at Astellas Pharma identified YM-155 as a highly potent, first-in-class survivin suppressant with potent antiproliferative activity against various human tumor cell lines (5). Phase II clinical trials in various types of cancer are currently in progress.

Preclinical Pharmacology

In vitro studies revealed that YM-155 selectively suppressed survivin expression in a gene promoter assay (IC_{50} = 0.54 nM), while having no effect on the expression of other IAP or Bcl-2 family proteins. YM-155 inhibited tumor cell viability and induced tumor cell apoptosis in a concentration-dependent manner in human hormone-refractory prostate cancer (HRPC) PC-3 cells at concentrations of 10-100 nM, while having no effect on the viability of human umbilical vein endothelial cells (HUVEC). The agent demonstrated promising antiproliferative activity against a panel of human tumor cell lines derived from HRPC, with GI_{50} values of 2.3-11 nM. *In vivo*, long-term continuous infusion of YM-155 was associated with greater efficacy and less systemic toxicity than i.v. bolus administration. Hematological and systemic toxicities of YM-155 were also milder compared to conventional chemotherapeutic agents (cisplatin, paclitaxel) at the corresponding

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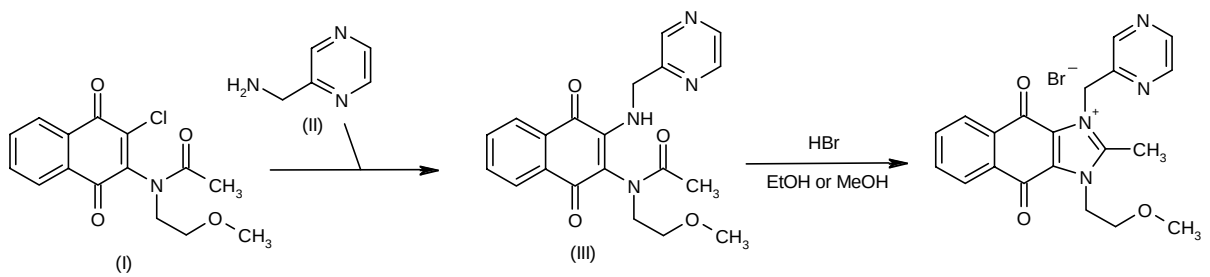
Scheme 1: Synthesis of YM-155



maximum tolerated dose (MTD). Three-day continuous infusion of YM-155 showed potent antitumor activity in an s.c.-xenografted PC-3 tumor model and reduced intratumoral survivin expression. In an orthotopic model of human prostate cancer, PC-3 tumor growth was almost completely inhibited by 3-day continuous infusion of YM-155 at 5 mg/kg. Analysis of YM-155 tissue distribution during a 3-day continuous infusion indicated higher distribution in tumor tissue (351-489 ng/g) than plasma (steady-state concentration of YM-155 = 18.4-23.7 ng/ml) (5-7).

The effect of infusion schedule on the antitumor activity of YM-155 was studied in mice bearing s.c. PC-3 xenografts. The mice received a fixed total dose of YM-155 as an i.v. bolus once or 3 times daily or as a continuous infusion. YM-155 administered by infusion showed significantly more potent antitumor activity, with > 100% tumor growth inhibition compared to 64% with bolus injections. Moreover, YM-155 infusion demonstrated significant and dose-dependent antitumor activity even at doses below the MTD, whereas conventional chemotherapeutic agents such as cisplatin and doxorubicin were only active at the MTD. Paclitaxel was almost as effective as YM-155 at the MTD in this study, but it was associated with a significant decrease in body weight (8).

The preclinical efficacy of YM-155 in experimental human lung tumor models was further evaluated both *in vitro* and *in vivo*. The agent suppressed the expression of survivin in human lung tumor cells and inhibited the growth of the cells with GI_{50} values of 1.5-540 nM. In human non-small cell lung cancer (NSCLC) Calu-6 and NCI-H358 xenograft models in mice, 168-h continuous infusion of YM-155 at doses of 3 and 10 mg/kg induced significant tumor regression without causing a decrease in body weight. Survivin suppression, induction of apoptosis in tumors and tumor regression caused by YM-155 occurred almost simultaneously (9).

Similar experiments were performed in murine models of diffuse large B-cell lymphoma (DLBCL, RL) and Burkitt's lymphoma (Ramos). A single administration of YM-155 as a 168-h continuous s.c. infusion at a dose of 1 or 3 mg/kg was repeated every 3 weeks. In mice bearing RL and Ramos lymphoma xenografts, YM-155 produced statistically significant tumor regression without body weight loss by day 21; the agent also suppressed survivin expression and induced cell death in the tumors. Four of 6 animals bearing RL tumors and 5 of 6 animals bearing Ramos tumors experienced complete tumor regression after treatment with YM-155. The antitumor efficacy of vincristine (0.5 mg/kg i.v.) and rituximab (50 mg/kg i.p.) was also evaluated in this study, but the two agents did not show greater antitumor activity or a survival benefit compared to YM-155 (10).

Using a panel of 127 human tumor cell lines, YM-155 demonstrated antiproliferative activity against 123 cell lines, with a mean log GI_{50} value of –7.85 (14 nM). The agent demonstrated marked activity against HRPC, melanoma, NSCLC, breast cancer, ovarian cancer, sarcoma, lymphoma and leukemia cell lines. The antiproliferative activity of YM-155 was not correlated with survivin expression or p53 status, and it showed similar activity against cell lines with normal, mutated or truncated p53. Drug resistance was observed in small cell lung cancer SHP-77, resistant breast cancer MCF7/ADR and MCF7/mdr1, and resistant human lung carcinoma A549 cell lines. Tumor regression at doses ranging from 1 to 10 mg/kg was observed in A-375 and SK-MEL-5 human malignant melanoma xenograft models, without a decrease in body weight (11).

Pharmacokinetics and Metabolism

The pharmacokinetics of YM-155 were evaluated in a phase I study conducted in 41 patients with advanced solid tumors. At the MTD (4.8 mg/m^2/day), the median clearance of YM-155 was 45.6 l/h, the median steady-state plasma concentration was 7.7 ng/ml and the median terminal half-life was 24 h (12-14).

The pharmacokinetics of YM-155 were further evaluated in a similar phase I study conducted in Japan. At the MTD (8.0 mg/m^2/day), the median clearance was 39 l/h, the median steady-state plasma concentration was 13 ng/ml and the median terminal half-life was 20 h (15).

Safety

YM-155 was well tolerated in both phase I studies. In the first study (12-14), the most frequent adverse events (AEs) included grade 1-2 pyrexia, arthralgia, nausea, fatigue and diarrhea and grade 3 or 4 drug-related AEs were mucosal inflammation (n=2), renal tubular necrosis (n=1) and transient neutropenia (n=1). Dose-limiting toxicity (DLT) consisted of 1 case each of reversible renal tubular necrosis with grade 3 mucositis and increased serum creatinine at 6 mg/m^2/day. In the Japanese study (15), 2 of 5 patients in the 10.6 mg/m^2/day dose group experienced DLT of increased blood creatinine during cycle 1, although both patients recovered to grade 1 or below in 2 weeks without plasma dialysis. The most frequent AEs included fatigue (39%), microalbuminuria (39%), pyrexia (33%) and anemia/decrease in hemoglobin (30%).

Generally good tolerance was also observed in a phase II study conducted in chemotherapy-naïve patients with unresectable stage III or IV melanoma (see Clinical Studies for further details). Four of 31 evaluable patients experienced serious AEs possibly or probably related to treatment, consisting of sepsis, headache and acute renal failure. The most frequent adverse events included fatigue (30.8%), nausea (30.8%), pyrexia (15.4%) and back pain (15.4%) (16, 17).

The safety and toxicity of YM-155 were evaluated in another phase II study conducted in patients with HRPC who previously received taxane chemotherapy. YM-155 showed an acceptable toxicity profile in this study. The most frequent AEs included fatigue (47%), nausea (31%) and anorexia (22%). Two patients discontinued the study because of AEs. Five patients experienced grade 3-5 drug-related AEs, including coagulopathy (grade 3) followed by intracranial hemorrhage (grade 5), fatigue (grade 3), upper respiratory tract infection (grade 3), decreased hemoglobin (grade 3) and thrombocytopenia (grade 3) (18, 19).

Preliminary data from a phase II study in 37 patients with advanced stage IIIB or IV NSCLC showed that 7 patients discontinued the study because of AEs, 4 of whom experienced elevated creatine kinase, fatigue, nausea, vomiting and allergic reactions which were considered to be related to YM-155. Another patient experienced grade 3 or 4 AEs, including cardiac arrhythmia, allergic reaction and fatigue, which were also considered to be drug-related, and the other 3 patients had procedure-related severe AEs. Fourteen patients discontinued the study because of progressive disease. Five patients died during the study, but none of the deaths was related to YM-155 treatment (20).

Clinical Studies

In addition to pharmacokinetics and safety, the phase I study in 41 patients with advanced solid tumors also examined the efficacy of YM-155 (1.8-6.0 mg/m^2/day by continuous i.v. infusion every 3 weeks). The most common tumor types evaluated in the study included prostate cancer (n=9), non-Hodgkin's lymphoma (NHL; n=5) and colorectal cancer (n=5). Three patients with NHL experienced partial responses (PRs), 1 of whom achieved a near-complete response (CR) and subsequently underwent bone marrow transplantation (BMT); the patient was back in remission for more than 14 months at the time of publication. The other 2 patients with NHL remained on treatment with YM-155 with sustained PRs. Two HRPC patients achieved a prostate-specific antigen (PSA) response (> 50% reduction), and 1 patient with NSCLC experienced a minor response (12-14).

In the Japanese phase I study (YM-155 1.8-10.6 mg/m^2/day), 9 patients experienced stable disease, 5 of whom achieved minor tumor shrinkage (15).

To evaluate the objective tumor response rate, including complete and partial responses defined by RECIST, progression-free survival and toxicity of YM-155 in the treatment of melanoma, a phase II study was conducted in 34 chemotherapy-naïve patients with unresectable stage III or IV melanoma (see above). YM-155 was administered as a 168-h continuous infusion every 3 weeks (1 cycle) at a dose of 4.8 mg/m^2/day. Clinical data from 31 evaluable patients demonstrated that YM-155 monotherapy was associated with an encouraging response rate. One patient achieved a CR at cycle 2 but progressed at cycle 8, another patient had a PR at cycle 12 and 7 patients had stable disease, for an overall disease control rate of 27% (16, 17).

As described above, another phase II study evaluated the PSA response (decline of > 50% from baseline) and objective response by RECIST in patients with HRPC who had previously received taxane chemotherapy. Patients received a 168-h continuous infusion every 3 weeks (1 cycle) at a dose of 4.8 mg/m^2/day. Preliminary data from 32 patients indicated that YM-155 was effective in the treatment of HRPC. At the time of reporting, 2 of the 32 patients were PSA responders: 1 achieved response at cycle 2 and the other at cycle 6 (18, 19).

The anticancer efficacy of YM-155 was also evaluated in the phase II study in patients with advanced stage IIIB or IV NSCLC who had failed previous therapy. The primary endpoint of the study was objective tumor response rate measured by RECIST and the secondary endpoints of the study were the progression-free survival rate and safety (see above). Patients received a 168-h continuous i.v. infusion every 3 weeks (1 cycle) at a dose of 4.8 mg/m^2/day for up to 6 cycles. Data on 37 patients with ECOG performance status of 0-2 were presented at the 5th International Symposium on Targeted Anticancer Therapies. One patient had a confirmed PR but subsequently progressed, and 15 patients experienced stable disease after 2 cycles (20).

Phase II clinical studies are in progress in patients with refractory DLBCL, NSCLC and unresectable stage III or metastatic stage IV melanoma (21-23).

Source

Astellas Pharma, Inc. (JP).

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