| Patent Right | Date | November 28, 2019 | Court | Intellectual Property High Court, Second Division |
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| | Case number | 2018 (Gyo-Ke) 10115 | | |
| - A case in which, with regard to the invention titled "NOVEL ANTIFOLATE COMBINATION THERAPIES", the court has determined that there is no motivation to further combine vitamin $B_{12}$ with the cited invention in which the combination of an antifolate and folic acid is administered.<br>- A case in which the court has determined that it cannot be acknowledged that the invention has been "publicly known" or "publicly worked" by Phase II clinical testing implemented in the foreign countries before the priority date. | | | | |

Case type: Rescission of Trial Decision to Maintain

Result: Dismissed

References: Article 29, paragraph (1), items (i) and (ii) and paragraph (2) of the Patent Act

Number of related rights, etc.: Patent No. 5102928, Patent No. 5469706

Summary of the Judgment

1. This case is a suit against the trial decision made by JPO that dismissed a demand for trial for invalidation against the patent, titled "NOVEL ANTIFOLATE COMBINATION THERAPIES". Plaintiff alleges errors in the determination of the novelty and the inventive step as grounds for rescission.

2. Regarding the inventive step, the court decision has determined as follows and maintained the finding and determination of the trial decision, stating that there is no motivation to further combine vitamin $B_{12}$ with the cited invention in which the combination of an antifolate and folic acid is administered.

(1) Each publicly known document only points out that homocysteine value at baseline of cancer patients (elevated by the deficiency of folic acid and/or vitamin $B_{12}$) was a predictor of the development of toxicity of one kind of antifolate of pemetrexed disodium (hereinafter referred to "MTA") as of the priority date. It cannot be acknowledged as a common general knowledge that "decreasing homocysteine level at baseline suppresses the development of toxicity and maintains antitumor activity" as Plaintiff alleges.

(2) Even if a person ordinarily skilled in the art should think that it was necessary to decrease homocysteine level at baseline below a threshold value of the development of toxicity of MTA of 10 μM for reducing toxicity risk of MTA, [i] As of the priority date, there was a document pointing out that there was a correlation between homocysteine level and the development of toxicity; however, there was no

correlation between methylmalonic acid level (elevated by the deficiency of vitamin $B_{12}$.) and the development of toxicity; and [ii] As of the priority date, the effects of the administration of vitamin $B_{12}$ on the functional status of folic acid in cancer patients were unclear, and it cannot be recognized that a person ordinarily skilled in the art had recognized that it is insufficient to supplement folic acid from the outside, but necessary to supplement even vitamin $B_{12}$ in order to normalize the functional state of folic acid in cancer patients. In view of this, it cannot be acknowledged that a person ordinarily skilled in the art would be motivated to add vitamin $B_{12}$.

3. Further, the court decision has generally determined as in follows and maintained the finding and determination of the trial decision, stating that it cannot be acknowledged that the invention according to the Patent was "publicly known" or "publicly worked" by a clinical test for cancer patients implemented in foreign countries before the priority date.

(1) While it can be assumed that in the clinical test there was an offer of information to patients to the extent that an anticancer agent to be administered is MTA, and it was administered in combination with folic acid and vitamin $B_{12}$, a guideline drafted by INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (hereinafter referred to as "ICH-GCP guideline") does not definitely specify "objective of the clinical test", "details of treatment in the clinical test", "procedure of the clinical test", and "reasonably expected benefit" to be described in the written agreement, etc. of informed consent, or to what extent information should be disclosed. It is also unclear from the evidences as to what law and regulation and practice were in effect at that time in foreign countries where the clinical test was implemented. Consequently, it cannot be acknowledged that information such as specific dose amounts, the timing and the route of administration of MTA, folic acid, and vitamin $B_{12}$, or information of "reducing toxicity associated with MTA administration while maintaining antitumor activity" was described in the written agreement, etc., going further from information reasonably deducible as being disclosed as above.

(2) ICH-GCP guideline 4.8.7 specifies that Investigator should answer questions from patients and their legally accepted representative (hereinafter collectively referred to as "patients and others") until patients and others are satisfied in getting agreement with patients; however, the provision of "should answer questions ... until patients and others are satisfied" is too abstract to find from the evidences that there were circumstances where all information including information such as specific dose amounts of MTA, folic acid, and vitamin $B_{12}$, the timing and the route of

administration, or information of "reducing toxicity associated with MTA administration while maintaining antitumor activity" was ready to be provided from Investigator to patients and others upon request from patients and others, let alone to find that all of these pieces of information were actually provided from Investigator upon request from patients and others.

Judgment rendered on November 28, 2019
2018 (Gyo-Ke) 10115 A case of seeking rescission of the JPO decision
Date of conclusion of oral argument: September 17, 2019

Judgment

Plaintiff Nipro Corporation

Defendant Eli Lilly and Company

Main text

1. The Plaintiff's claim shall be dismissed.
2. Plaintiff shall bear the court costs.

Facts and reasons

No. 1 Claim

The trial decision for Invalidation Trial No. 2014-800208 case that the JPO rendered on July 4, 2018 shall be rescinded.

No. 2 Summary of the case

This case is a suit against trial decision that dismissed a demand for trial for patent invalidation. The issue is the presence or absence of inventive step and novelty.

1. History of the procedures

Defendant filed a patent application titled "NOVEL ANTIFOLATE COMBINATION THERAPIES" on June 15, 2001 (Patent Application No. 2002-506715, Priority date claimed: June 30, 2000 [hereinafter referred to as "first priority claiming", the priority date is "first priority date"] Priority date claimed: September 27 of the same year [hereinafter referred to as "second priority claiming", the priority date is "second priority date"] April 18, 2001 [hereinafter referred to as "third priority date"], United States, Exhibits Ko 31, 32), and the patent right was registered on October 5, 2012 (Patent No. 5102928) (hereinafter referred to as "the Patent", and the description and the drawing of the Patent is referred to as "the description". Exhibit Ko 201).

Plaintiff sought a demand for invalidation trial of the Patent on December 16, 2014 (Invalidation Trial No. 2014-800208), and the JPO made a trial decision to the effect that "the demand for trial of the case was groundless" on July 4, 2018 (Hereinafter referred to as "the trial decision") and its certified copies were served to

Plaintiff on 12th day of the same month.

2. Gist of the Invention

Claims 1 to 7 of the Patent (Hereinafter the invention of each claim is referred to as "Invention 1", etc. according to the number of the claim, and the inventions of the claims are collectively referred to as "the Invention" in some cases) are set forth as below:

[Claim 1]

An agent for reducing toxicities and maintaining antitumor activity with respect to administration of pemetrexed disodium, the agent comprising folic acid and vitamin $B_{12}$,

wherein the effective amount of pemetrexed disodium is administered in combination with about 0.1 mg to about 30 mg of folic acid and about 500 μg to about 1500 μg of vitamin $B_{12}$, wherein said vitamin $B_{12}$ is administered about one to three weeks before the first administration of pemetrexed disodium, and the administration of said vitamin $B_{12}$ is repeated about every 6 weeks to about every 12 weeks during pemetrexed disodium administration.

[Claim 2]

The agent of Claim 1, wherein vitamin $B_{12}$ is administered in an amount of about 1000 μg.

[Claim 3]

The agent of Claim 1 or 2, wherein vitamin $B_{12}$ is administered through intramuscular injection, or oral or parenteral formulation.

[Claim 4]

The agent of Claim 3, wherein vitamin $B_{12}$ is administered via intramuscular injection.

[Claim 5]

The agent of Claim 3, wherein vitamin $B_{12}$ is orally administered.

[Claim 6]

An agent for reducing toxicities and maintaining antitumor activity with respect to administration of pemetrexed disodium, the agent comprising folic acid and vitamin $B_{12}$,

wherein the effective amount of pemetrexed disodium is administered in combination with about 0.1 mg to about 30 mg of folic acid and about 500 μg to about 1500 μg of vitamin $B_{12}$, wherein said vitamin $B_{12}$ is administered by intramuscular injection, wherein said vitamin $B_{12}$ is administered about one to three weeks before the first administration of pemetrexed disodium, and the administration of said

vitamin $B_{12}$ is repeated about every 6 weeks to about every 12 weeks during pemetrexed disodium administration.

[Claim 7]

An agent for reducing toxicities and maintaining antitumor activity with respect to administration of pemetrexed disodium, the agent comprising folic acid and vitamin $B_{12}$,

wherein the effective amount of pemetrexed disodium is administered in combination with about 0.1 mg to about 30 mg of folic acid and about 500 μg to about 1500 μg of vitamin $B_{12}$, wherein the treatment using said vitamin $B_{12}$ is administered by intramuscular injection or orally, and is repeated about every 24 hours to about every 1680 hours until the treatment using pemetrexed disodium is ceased.

3. Abstract of reasons of trial decision

(1) Reason 1 for invalidation (Lack of inventive step)

A. Invention described in Exhibit Ko 1 (Unexamined Patent Application Publication No. 1993-97705) (hereinafter referred to as "Exhibit Ko 1 invention".)

Exhibit Ko 1 describes the invention of "a toxicity alleviating agent for reducing toxicity while maintaining therapeutic effects of GAR-transformylase, comprising an active ingredient of folic acid, wherein the effective amount of GAR-transformylase inhibitor is administered in combination with about 0.5 mg/day to about 30 mg/day of folic acid." (Exhibit Ko 1 invention).

B. Comparison and the determination of different features between Invention 1 and Exhibit Ko 1 invention

(A) Common feature

Invention 1 and Exhibit Ko 1 invention have in common that they are the invention of "An agent comprising folic acid for reducing toxicity associated with the administration of GAR-transformylase inhibitor and maintaining antitumor activity, wherein the effective amount of GAR-transformylase inhibitor is administered in combination with about 0.1 mg to about 30 mg of folic acid."

(B) Different features

[Different Feature 1]

Invention 1 uses "pemetrexed disodium" as an inhibitor of GAR-transformylase, whereas Exhibit Ko 1 invention does not use "pemetrexed disodium".

[Different Feature 2]

Invention 1 further comprises vitamin $B_{12}$, whereas Exhibit Ko 1 invention does not contain vitamin $B_{12}$.

[Different Feature 3]

Invention 1 administers an effective amount of pemetrexed disodium further in combination with about 500 μg to about 1500 μg of vitamin $B_{12}$, wherein said vitamin $B_{12}$ is administered about one to three weeks before the first administration of pemetrexed disodium, and said vitamin $B_{12}$ is administered with a specific dosage and dose regimen in combination by repeating about every 6 weeks to about every 12 weeks during pemetrexed disodium administration. Exhibit Ko 1 invention does not administer vitamin $B_{12}$ with the above specific dosage and dose regimen in combination.

(C) Determination about the different features

a. Regarding Different Feature 1

Exhibit Ko 1 is silent about the use of pemetrexed disodium salt (hereinafter sometimes referred to "LY231514 (MTA)", "MTA", or "ALIMTA") as a GAR-transformylase inhibitor; however, Exhibit Ko 1 describes that "every compound found to inhibit GAR-transformylase or the other folate-requiring enzyme are subjected to the treatment of the present invention" (Exhibit Ko 1, paragraph [0006]). Thus it can be said that Exhibit Ko 1 invention can also use the other GAR-transformylase inhibitor as well as Lometrexol described in Exhibit Ko 1 as a "GAR-transformylase inhibitor".

On the other hand, Exhibit Ko 5 (Hilary Calvert, "An Overview of Folate Metabolism: Features Relevant to the Action and Toxicities of Antifolate Anticancer Agents", Seminars in Oncology, Volume 26, No. 2, Supplement 6, 1999) describes LY231514 (MTA) together with Lometrexol (DDAT HF) of Exhibit Ko 1 as a specific example of various antifolates, and describes that LY231514 (MTA) has a promising level of activity as reported in an initial Phase II clinical test, and LY231514 (MTA) is thought to be an important agent superior to the existing drug.

Consequently, it can be said that a person ordinarily skilled in the art who read the description of Exhibits Ko 1 and Ko 5 could have naturally conceived of using LY231514 (MTA) described in Exhibit Ko 5 as "GAR-transformylase inhibitor" of Exhibit Ko 1 invention.

b. Regarding Different Feature 2

Exhibit Ko 1 does not describe or suggest further containing the other active ingredient in Exhibit Ko 1 invention.

Further, none of Exhibits Ko 5, Ko 6 (C. Niyikiza et al., "MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity" Annals of Oncology, Volume 9, Supplement 4, 1998) and Exhibit Ko 7 (C. Niyikiza et al., "LY231514 (MTA): RELATIONSHIP OF VITAMIN

METABOLITE PROFILE TO TOXICITY", Proceedings of ASCO (American Society of Clinical Oncology) Volume 17, 1998) describes taking any measure to reduce plasma homocysteine level for reducing the development of toxicity of MTA. As described in Exhibits Ko 8 to 16, it was common general knowledge as of the earliest priority date of the Patent of June 30, 2000 (first priority date, hereinafter referred to as "the priority date") that the administration of vitamin $B_{12}$ results in lowered plasma homocysteine level, and the coadministration of folic acid and vitamin $B_{12}$ results in further decreased plasma homocysteine level compared to the case of the single dose of folic acid; however, the coadministration of vitamin $B_{12}$ or folic acid and vitamin $B_{12}$ is neither described nor suggested for reducing the development of toxicity of MTA or the other antifolate.

Therefore, it cannot be said that a person ordinarily skilled in the art who considered the common technical knowledge as of the priority date in addition to the descriptions of Exhibits Ko 1 and Ko 5 could have easily conceived of further containing vitamin $B_{12}$ as a means for reducing homocysteine level in Exhibit Ko 1 invention with a focus on plasma homocysteine level before the treatment in using LY231514 (MTA) described in Exhibit Ko 5 as a "GAR-transformylase inhibitor" of Exhibit Ko 1 invention.

c. Regarding Different Feature 3

It cannot be said that a person ordinarily skilled in the art who considers the common technical knowledge as of the priority date in addition to the description of Exhibits Ko 1 and Ko 5 could have easily conceived of using Exhibit Ko 1 invention together with vitamin $B_{12}$. It thus cannot be said that a person ordinarily skilled in the art could have easily conceived of Invention 1 which comprises further administering vitamin $B_{12}$ in combination with the specific dose and dose regimen on the basis of Exhibit Ko 1 invention.

C. Inventions 2 to 7

Inventions 2 to 5 directly or indirectly depend from Invention 1 to further limit the dose and dosage regimen of vitamin $B_{12}$ in Invention 1 and differ from Exhibit Ko 1 invention in that the former contains Different Features 1 and 2 and a different feature that only differs slightly from Different feature 3 in details.

Further, Inventions 6 and 7 differ from Exhibit Ko 1 invention in that the former contains Different Features 1 and 2 and a different feature that only differs slightly from Different Feature 3 in details.

Therefore, similarly to Invention 1, it cannot be said that any of the Inventions was easily conceivable by a person ordinarily skilled in the art on the basis of the

inventions described in Exhibits Ko 1 and Ko 5 and the state of art or the common general knowledge as of the priority date.

D. Effects of the Invention

Even in view of the state of the art and the common general knowledge as of the priority date in addition to the descriptions of Exhibits Ko 1 and Ko 5, there is no evidence from which one can infer what kind of effect is caused against the development of toxicity and its antitumor activity associated with the administration of pemetrexed disodium in a case of administering folic acid and vitamin $B_{12}$ in combination with the administration of pemetrexed disodium. Therefore, it cannot be said that a person ordinarily skilled in the art could expect the effects of the Invention.

E. Summary

Therefore, Inventions 1 to 7 are not the invention which were easily conceivable by a person ordinarily skilled in the art on the basis of the inventions described in Exhibits Ko 1 and Ko 5 and the state of art or the common general knowledge as of the priority date.

(2) Reason 2 for invalidation (Lack of novelty)

Plaintiff alleges that the Invention was a publicly known invention or a publicly worked invention in a foreign country before the priority date, on the basis of Phase II clinical test (H3E-MC-JMDR test, hereinafter referred to as "the present clinical test") mentioned in Exhibits Ko 21 to 23. Applying the provision of ICH harmonized trilateral guideline (Exhibit Ko 36, hereinafter referred to as "ICH-GCP guideline") for GCP (good clinical practice) drafted by INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE to the present clinical test, it is recognized that a person who was regarded as a "patient supplemented by vitamin" in the present clinical test could know all the clinical test protocol information including numerical values of the specific dose amount, dose period and administration route of folic acid, vitamin $B_{12}$, and pemetrexed disodium to be used in "vitamin supplemented regimen" when having access to Investigator.

First of all, it should be determined with consideration for the result of the assessment of the effectiveness and safety of "vitamin supplementation regimen" by collecting the result obtained from individual patients who participated in the present clinical test and statistically processing as to whether or not "vitamin supplementation regimen" might be a regimen that could satisfy a matter specifying the invention essential for Invention 1 of "reducing toxicities and maintaining antitumor activity

with respect to administration of pemetrexed disodium". Therefore, it cannot be said as of June 29, 2000, one day before the priority date, that "a patient supplemented by vitamin" who participated in the present clinical test could know information that the "vitamin supplementation regimen" might be a regimen that could satisfy a matter specifying the invention essential for Invention 1 of "reducing toxicities and maintaining antitumor activity with respect to administration of pemetrexed disodium".

Therefore, Invention 1 corresponds to neither a "publicly known invention" nor a "publicly worked invention".

Further, in view of the foregoing, similarly to Invention 1, none of Inventions 2 to 7 corresponds to a "publicly known invention" or a "publicly worked invention".

4. Reasons for cancellation of trial decision presented by Plaintiff

(1) Errors in the determination of lack of inventive step (Reason 1 for rescission)

(2) Errors in the determination of lack of novelty (Reason 2 for rescission)

(omitted)

No. 4 Judgment of this court

1. The Invention

(1) The description

[0001]

(Background Art)

Potentially, life-threatening toxicity remains a major limitation to the optimal administration of antifolates. (See, for general information, Antifolate Drugs in Cancer Therapy, edited by Jackman, Ann L., Humana Press, Totowa, NJ, 1999.) In some cases, a supportive intervention is routinely used to permit safe, maximal dosing. For example, steroids, such as dexamethone, can be used to prevent the formation of skin rashes caused by the antifolate. (Antifolate, page 197.)

[0002]

Antifolates represent one of the most thoroughly studied classes of antineoplastic agents, with aminopterin initially demonstrating clinical activity approximately 50 years ago. Methotrexate was developed shortly thereafter, and today is a standard component of effective chemotherapeutic regimens for malignancies such as lymphoma, breast cancer, and head and neck cancer (...). Antifolates inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways; in particular, thymidylate synthase ("TS"), dihydrofolate reductase

("DHFR"), and glycinamide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. (...). Several antifolate drugs are currently in development. Examples of antifolates that have thymidylate synthase inhibiting ("TSI") characteristics include 5-fluorouracil and Tomudex (registered trademark). An example of an antifolate that has dihydrofolate reductase inhibiting ("DHFRI") characteristics is Methotrexate (registered trademark). An example of an antifolate that has glycinamide ribonucleotide formyltransferase inhibiting ("GARFTI") characteristics is Lometrexol. Many of these antifolate drugs inhibit more than one biosynthetic pathway. For example, Lometrexol is also an inhibitor of dihydrofolate reductase and pemetrexed disodium salt (Alimta, Eli Lilly and Company, Indianapolis, IN) and has demonstrated thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase inhibition.

[0003]

A limitation to the development of these drugs is that the cytotoxic activity and subsequent effectiveness of antifolates may be associated with substantial toxicity for some patients. Additionally, antifolates as a class are associated with sporadic severe myelosuppression with gastrointestinal toxicity which, although infrequent, carries a high risk of mortality. The inability to control these toxicities led to the abandonment of clinical development of some antifolates and has complicated the clinical development of others, such as Lometrexol and raltitrexed (...).

[0004]

Initially, folic acid was used as a treatment for toxicities associated with GARFTI. See, e.g., U.S. Patent No. 5,217,974. Folic acid has been shown to lower homocysteine levels (...), and homocysteine levels have been shown to be a predictor of cytotoxic events related to the use of GARFT inhibitors; see, e.g., U.S. Patent No. 5,217,974. However, even with this treatment, cytotoxic activity of GARFT inhibitors and antifolates as a class remains a serious concern in the development of antifolates as pharmaceutical drugs. The ability to lower cytotoxic activity would represent an important advance in the use of these agents.

[0005]

Surprisingly and unexpectedly, we have now discovered that certain toxic effects such as mortality, and nonhematologic events, such as skin rashes and fatigue, caused by antifolates, as a class, can be significantly reduced by the presence of a methylmalonic acid lowering agent, without adversely affecting therapeutic efficacy. The present invention thus provides a method for improving the therapeutic utility of antifolate drugs by administering to the host undergoing treatment a methylmalonic

acid lowering agent. We have discovered that increased level of methylmalonic acid is a predictor of toxic events in patients that receive an antifolate drug and that treatment for the increased methylmalonic acid, such as treatment with vitamin $B_{12}$, reduces mortality and nonhematologic events, such as skin rashes and fatigue events, previously associated with the antifolate drugs.

[0006]

Additionally, we have discovered that the combination of a methylmalonic acid lowering agent and folic acid synergistically reduces the toxic events associated with the administration of antifolate drugs. Although the treatment and prevention of cardiovascular disease with folic acid in combination with vitamin 12 (Court decision's note: maybe a typo of "vitamin B12") is known, the use of the combination for the treatment of toxicity associated with the administration of antifolate drugs was unknown heretofore.

[0007]

The present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

[0008]

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal, comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent.

[0009]

Furthermore, the present invention relates to a method of inhibiting tumor growth in mammals, comprising administering to said mammals an effective amount of an antifolate in combination with a methylmalonic acid lowering agent.

[0010]

Furthermore, the present invention relates to a method of administering an antifolate to a mammal in need thereof, comprising administering an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and an FBP binding agent. A preferred FBP binding agent is folic acid.

[0011]

Furthermore, the present invention relates to a method of reducing the toxicity associated with the administration of an antifolate to a mammal, comprising administering to said mammal an effective amount of said antifolate in combination with a methylmalonic acid lowering agent and an FBP binding agent. A preferred

FBP binding agent is folic acid.

[0018]

The current invention concerns the discovery that administration of a methylmalonic acid lowering agent in combination with an antifolate drug reduces the toxicity of the said antifolate drug.

[0019]

The term "inhibit" as it relates to antifolate drugs refers to prohibiting, alleviating, ameliorating, halting, restraining, slowing or reversing the progression of, or reducing tumor growth.

[0020]

As used herein, the term "effective amount" refers to an amount of a compound or drug, which is capable of performing the intended result. For example, an effective amount of an antifolate drug that is administered in an effort to reduce tumor growth is that amount that is required to reduce tumor growth.

[0021]

As used herein, the term "toxicity" refers to a toxic event associated with the administration on an antifolate. Such events include, but are not limited to, neutropenia, thrombopenia, toxic death, fatigue, anorexia, nausea, skin rash, infection, diarrhea, mucositis, and anemia. For further explanation of the types of toxicity experienced by patients receiving antifolates, see, for general information, Antifolate Drugs in Cancer Therapy. Preferably, toxicity refers to toxic death, fatigue, neutropenia, thrombopenia, and mucositis.

[0023]

As used herein, the term "in combination with" refers to the administration of the methylmalonic acid lowering agent, the antifolate drug, and optionally the folic acid; in any order such that sufficient levels of methylmalonic acid lowering agent and optionally folic acid are present to reduce the toxicity of an antifolate in a mammal. The compounds may be administered simultaneous as a single composition or as two separate compositions, or can be administered sequentially as separate compositions such that an effective amount of the agent first administered is in the patient's body when the second and/or third agent is administered. The antifolate drug may be administered to the mammal first, followed by treatment with the methylmalonic acid lowering agent. Alternatively, the mammal may be administered the antifolate drug simultaneously with the methylmalonic acid lowering agent. Preferably, the mammal is pretreated with the methylmalonic acid lowering agent and then treated with the antifolate. If folic acid is to be administered in addition to the

methylmalonic acid lowering agent, the folic acid may be administered at any time prior, post, or simultaneously to the administration of either the methylmalonic acid lowering agent or the antifolate. Preferably, the mammal is pretreated with the methylmalonic acid, and then treated with folic acid, followed by treatment with the antifolate compound.

[0024]

The terms "antifolate" and "antifolate drug" refer to a chemical compound which inhibits at least one key folate-requiring enzyme of the thymidine or purine biosynthetic pathways, preferably thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), or glycinamide ribonucleotide formyltransferase ("GARFT"), by competing with reduced folates for binding sites of these enzymes. Preferred examples of antifolates include 5-fluorouracil, as manufactured by Glaxo; Tomudex (registered trademark), as manufactured by Zeneca; Methotrexate (registered trademark), as manufactured by Lederle; Lometrexol (registered trademark), as manufactured by Tularik; pyrido [2,3-d] pyrimidine derivatives described by Taylor et al. in U.S. Pat Nos. 4684653, 4833145, 4902,96, 4871743, and 4882334; derivatives described by Akimoto in U.S. Pat No. 4997838; thymidylate synthase inhibitors as found in EPO Application 239,362; and most preferred, Pemetrexed Sodium (ALIMTA), as manufactured by Eli Lilly & Co.

[0025]

The terms "methylmalonic acid" and "MMA" refer to a structural isomer of succinic acid present in minute amounts in healthy human urine.

[0026]

The term "methylmalonic acid lowering agent" refers to a substrate, which lowers the concentration of methylmalonic acid in a mammal. A preferred example of such a substrate is vitamin B12. ...

[0027]

The term "vitamin B12" refers to vitamin B12 and its pharmaceutical derivatives, such as hydroxocobalamin, cyano-10-chlorocobalamin, aquocobalaminperchlorate, aquo-10-chlorocobalamin perchlorate, azidocobalamin, chlorocobalamin, and cobalamin. Preferably the term refers to vitamin B12, cobalamin, and chlorocobalamin.

[0029]

The skilled artisan will appreciate that the methylmalonic lowering agents are effective over a wide dosage range. For example, when cobalamin is used as the methylmalonic lowering agent, the dosage of cobalamin may fall within the range of

about 0.2 μg to about 3000 μg of cobalamin from once daily for a month to once every nine weeks for a year. Preferably, cobalamin will be dosed as an intramuscular injection of about 500 μg to about 1500 μg administered from about every 24 hours to about every 1680 hours. Preferably, it is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to administration of the antifolate and repeated from about every 24 hours to about every 1680 hours, regardless of when treatment with the antifolate is started and continued until the administration of the antifolate is discontinued. Most preferred is an intramuscular injection of about 1000 μg administered initially from about 1 to about 3 weeks prior to the first administration of the antifolate and repeated every 6 to 12 weeks, preferably about every 9 weeks, and continued until the discontinuation of the antifolate administrations. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

[0030]

The term "FBP binding agent" as used herein refers to a folic binding protein binding agent which includes folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof. ...

[0032]

The FBP binding agent to be utilized according to this invention can be in its free acid form, or can be in the form of a physiologically-acceptable salt or ester which is converted to the parent acid in a biological system. The dosage generally will be provided in the form of a vitamin supplement; namely, as a tablet administered orally, preferably as a sustained release formulation, as an aqueous solution added to drinking water, an aqueous parenteral formulation, e. g., an intravenous formulation, or the like.

[0033]

The FBP binding agent is usually administered to the subject mammal prior to treatment with the antifolate. Pretreatment with the suitable amount of FBP binding

agent from about 1 to about 24 hours is usually sufficient to substantially bind to and block the folate binding protein prior to administration of the antifolate. Although one single dose of the FBP binding agent, preferably an oral administration of folic acid, should be sufficient to load the folate binding protein, multiple dosing of the FBP binding agent can be employed for periods up to weeks before treatment with the active agent to ensure that the folate binding protein is sufficiently bound, in order to maximize the benefit derived from such pretreatment.

[0034]

In the especially preferred embodiment of this invention, about 0.1 mg to about 30 mg, most preferably about 0.3 mg to about 5 mg, of folic acid is administered orally to a mammal about 1 to 3 weeks post administration of the methylmalonic acid lowering agent and about 1 to about 24 hours prior to the parenteral administration of the amount of an antifolate. However, it will be understood that the amount of the methylmalonic acid lowering agent actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual agent administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect.

(2) Summary of the Invention

According to the recitation of the Claims of the Patent of the aforesaid No. 2-2 and the description of the specification of the aforesaid (1), the Invention is recognized as follows:

The present invention concerns the discovery that administration of a methylmalonic acid lowering agent in combination with an antifolate drug reduces the toxicity of said antifolate drug (paragraph [0018]).

Antifolates are one type of antimalignant tumor drug that inhibits one or several key folate metabolism-requiring enzymes of the thymidine and purine biosynthetic pathways, in particular, thymidylate synthase "TS", dihydrofolate reductase "DHFR", and glycinamide ribonucleotide formyltransferase "GARFT", by competing with reduced folates for binding sites of these enzymes (paragraph [0002]). Antifolates have cytotoxicity and are associated with sporadic severe myelosuppression with gastrointestinal toxicity which carries a high risk of mortality. This led to the abandonment of clinical development of some antifolates and has

complicated the clinical development (paragraph [0003]).

The Invention has an objective to suppress tumor growth, while reducing toxicity (neutropenia, thrombopenia, toxic death, fatigue, anorexia, nausea, skin rash, infection, diarrhea, mucositis, anemia, etc.) caused by pemetrexed disodium ([Claim 1] to [Claim 7], paragraphs [0008], [0009], and [0019] to [0021]).

In the past, folic acid has been used for the treatment of toxicity associated with one kind of antifolate of a GARFT inhibitor, and homocysteine value is a barometer of the development of toxicity associated with the use of a GARFT inhibitor. The inventors of the Invention have found that the elevation of methylmalonic acid level is a forerunner of toxic events of antifolates, and the measure of using vitamin $B_{12}$, etc. may decrease death rate associated with antifolates, non-hematological events (cutaneous eruption, fatigue, etc.), and furthermore, the combination of methylmalonic acid lowering agent and folic acid may synergistically decrease toxic events associated with antifolates (paragraphs [0004] to [0006]), and to solve the above problem, the inventors have adopted the combination of folic acid and vitamin $B_{12}$ as an agent for reducing toxicity associated with the administration of pemetrexed disodium and maintaining antitumor activity, and specified the dose amount, the timing, and the route of administration of folic acid and vitamin $B_{12}$ ([Claim 1] to [Claim 7]).

(3) Priority date of the Patent

Plaintiff alleges that [i] the description of the application on which the first priority claiming is based (Exhibit Ko 31) neither describes nor suggests the invention to administer in combination with "about 0.1 mg to about 30 mg folic acid" and [ii] the description of the application on which the second priority claiming is based (Exhibit Ko 32) does not describe the result of the clinical test of the paragraph [0060] of the description, and in view of the foregoing, the earliest priority date of the Patent is the third priority date of April 18, 2001, and in the determination of the inventive step a consideration should be given to Exhibits Ko 33, 51, 52, the publicly known documents published between the second priority date of September 27, 2000 and the third priority date.

Exhibit Ko 32 (page 7, line 3 from the bottom to page 8, line 2, its translation of Exhibit Ko 32-1, page 7, lines 8 to 10) explicitly describes "about 0.1 mg to about 30 mg" for an amount of folic acid to be administered, and Exhibit Ko 32 also describes the other part of the Invention. Thus the Patent can claim priority based on at least the second priority date. The description of paragraph [0060] of the description is a description of the examples. Should a part of the description of such

examples not be described in Exhibit Ko 32, this would not be sufficient to render the priority claiming based on Exhibit Ko 32 moot.

Further, as aforementioned, Exhibits Ko 33, 51, 52 presented by Plaintiff were published between the second priority date and the third priority date, and thus the Invention can claim priority based on, at the latest, the second priority date. Therefore, these publications should not be considered in the determination of the inventive step.

2. Reason 1 for Rescission (Errors in the finding and the determination of Lack of Inventive step)

(1) Finding of Exhibit Ko 1 invention

A. Exhibit Ko 1 has the following descriptions:

[Title of the Invention] Improved therapeutic drug

[Claim 1] A toxicity-reducing agent for other antifolates that bind to GAR-transformylase inhibitor or folic acid binding protein, comprising an active ingredient of a folic acid binding protein binder selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, and a physiologically available salt or ester thereof.

[Claim 2] The toxicity-reducing agent of Claim 1, wherein the binder is folic acid or a physiologically available salt or ester thereof.

[Claim 3] The toxicity-reducing agent of Claim 1 or 2, wherein the GAR-transformylase inhibitor is Lometrexol.

[Claim 4] A cancer chemotherapeutic agent comprising folic acid or a physiologically available salt or ester thereof in combination with Lometrexol.

[Detailed Description of the Invention]

[0001] The present invention relates to a new use of folic acid and a related compound thereof for decreasing toxicity while maintaining therapeutic effects of an antitumor antifolate drug.

[0002]

Antifolates represent one of the most thoroughly studied classes of antineoplastic agents, with aminopterin initially demonstrating clinical activity approximately 50 years ago. Methotrexate was developed shortly thereafter, and today is a standard component of effective chemotherapeutic regimens for malignancies such as lymphoma, breast cancer, and head and neck cancer (...). Antifolates inhibit one or several key folate-requiring enzymes of the thymidine and purine biosynthetic pathways, in particular, thymidylate synthase ("TS"), dihydrofolate reductase ("DHFR"), and glycinamide ribonucleotide formyltransferase ("GARFT"), by

competing with reduced folates for binding sites of these enzymes. (...). Several antifolate drugs are currently in development. Examples of antifolates that have thymidylate synthase inhibiting ("TSI") characteristics include 5-fluorouracil and Tomudex (registered trademark). An example of an antifolate that has dihydrofolate reductase inhibiting ("DHFRI") characteristics is Methotrexate (registered trademark). An example of an antifolate that has glycinamide ribonucleotide formyltransferase inhibiting ("GARFTI") characteristics is Lometrexol. Many of these antifolate drugs inhibit more than one biosynthetic pathway. For example, Lometrexol is also an inhibitor of dihydrofolate reductase and pemetrexed disodium (Alimta (registered trademark), Eli Lilly and Company, Indianapolis, IN) and has demonstrated inhibition of thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase.

[0002] Lometrexol is the generic name given to 5,10-dideazatetrahydrofolic acid, also referred to as DDATHF. Lometrexol is a member of a new class of antitumor agents that have been found to specifically inhibit glycinamide ribonucleotide (GAR) transformylase, an enzyme required in the initial stages of purine biosynthesis, ... GAR-transformylase inhibitors are also known to be useful in treating conditions such as gout, psoriasis, mycosis fungoides, autoimmune disorders, rheumatoid arthritis, and other inflammatory disorders, and during organ transplantation and under other related immunosuppressant related conditions.

[0003] Lometrexol has been studied clinically and shown to be a potent antitumor agent, especially against solid tumors such as colorectal, lung, breast, head and neck, and pancreatic; ... Like most other antitumor agents, Lometrexol exhibits some undesirable side effects, in addition to its efficacy against tumors; ... Typical side effects observed to date include anorexia, weight loss, mucositis, leukopenia, anemia, hypoactivity, and dehydration.

[0004] We have now discovered that the toxic effects of lometrexol and related GAR-transformylase inhibitors and other antifolate agents which bind to folate binding protein (FBP) (...) can be significantly reduced by the presence of an FBP binding agent, without adversely affecting therapeutic efficacy. The present invention thus provides a method for improving the therapeutic utility of GAR-transformylase inhibitors and other antifolates by coadministering an FBP binding agent to the host undergoing treatment.

[0005] In one aspect of this invention, we provide a method of inhibiting the growth of GAR-transformylase-dependent tumors in mammals, comprising administering to said mammals an effective amount of a GAR-transformylase inhibitor or other

antifolate which binds to an FBP, in combination with a toxicity-reducing amount of an FBP binding agent, or a physiologically-available salt or ester thereof. The invention more particularly provides a method for reducing the mammalian toxicity of a GAR-transformylase inhibitor or other antifolate which binds to an FBP, which comprises administering a toxicity-reducing amount of an FBP binding agent or a physiologically-available salt or ester thereof to the mammal receiving treatment. In particular, there is provided a method for reducing the toxicity of a GAR-transformylase inhibitor or other antifolate which binds to an FBP in a mammal, which comprises pretreating the mammal with an amount of a compound selected from folic acid, (6R)-5-methyl-5,6,7,8-tetrahydrofolic acid, and (6R)-5-formyl-5,6,7,8-tetrahydrofolic acid, or a physiologically-available salt or ester thereof, sufficient to have substantially blocked the FBP before administration of the antifolate. In the most preferred embodiment of the invention, Lometrexol is administered to a subject suffering from a solid tumor or other type of cancer and in need of treatment, after pretreatment with folic acid, thereby reducing toxic effects of Lometrexol while maintaining good antitumor activity.

[0006] The invention provides a method for reducing the toxicity of GAR-transformylase inhibitors or other antifolates that bind to an FBP that is found in biological systems by the prior administration of an FBP binding agent or a physiologically-available salt or ester thereof. GAR-transformylase inhibitors and related antifolates are those compounds which effectively inhibit the physiological actions of the enzyme known as glycinamide ribonucleotide transformylase. This enzyme is well known to be required in the initial stages of purine biosynthesis in mammals, which is implicated in DNA synthesis. Interruption of this biosynthetic pathway causes a disturbance in DNA synthesis and consequently causes cell death. Any compound which is shown to inhibit the GAR-transformylase or other folate-requiring enzyme is subject to treatment in accordance with this invention.

[0012] Folic acid is a vitamin which is required by mammals for proper regeneration of the blood-forming elements and their functioning, and as a coenzyme is involved in intermediary metabolic processes in which one-carbon units are transferred. These reactions are important in interconversions of various amino acids and in purine and pyrimidine synthesis. Folic acid is commonly supplied to diets of humans via consumption of food sources such as liver, kidney, dry beans, asparagus, mushrooms, broccoli, lettuce, milk, and spinach, as well as by vitamin supplements. The minimum amount of folic acid commonly required by normal adults is about 0.05 mg/day. According to this invention, folic acid, or a physiologically-available salt or

ester thereof, is administered to a human subject at a dose of about 0.5 mg/day to about 30 mg/day to diminish the toxic effects of a GAR-transformylase inhibitor or other antifolate also being administered to such subject. In a preferred embodiment, folic acid will be administered at about 1 to about 5 mg/day together with the normal dosing of a GAR-transformylase inhibitor such as lometrexol.

[0015] The FBP binding agent to be utilized according to this invention can be in its free acid form, or can be in the form of a physiologically-acceptable salt or ester which is converted to the parent acid in a biological system. The dosage generally will be provided in the form of a vitamin supplement; namely, as a tablet administered orally, preferably as a sustained release formulation, as an aqueous solution added to drinking water, an aqueous parenteral formulation, e.g., an intravenous formulation, or the like.

[0016] The FBP binding agent is administered to the subject mammal prior to treatment with the GAR-transformylase inhibitor or other antifolate. Pretreatment with the suitable amount of FBP binding agent from about 1 to about 24 hours in advance is usually sufficient to substantially bind to and block the folate binding protein prior to administration of the GAR-transformylase inhibitor or other antifolate. Although one single dose of the FBP binding agent, preferably an oral administration of folic acid, should be sufficient to load the folate binding protein, multiple dosing of the FBP binding agent can be employed for periods up to weeks before treatment with the active agent to ensure that the folate binding protein is sufficiently bound in order to maximize the benefit derived from such pretreatment.

[0017] In the especially preferred embodiment of this invention, about 1 mg to about 5 mg of folic acid is administered orally to a mammal about 1 to about 24 hours prior to the parenteral administration of the amount of lometrexol which is normally required to attain the desired therapeutic benefit. Although greater or additional doses of folic acid or another FBP binding agent are also operable, the above parameters will usually bind the folate binding protein in an amount sufficient to reduce the toxicity effects normally seen upon lometrexol administration above.

[0018] It should be noted that the FBP binding agent is not an antitumor agent and that the pretreatment of a mammal with an FBP binding agent does not provide a synergistic or potentiating effect. Rather, by having substantially bound the folate binding protein with an FBP binding agent prior to administration of the GAR-transformylase inhibitor or other antifolate, the toxic effects of such subsequent treatment are greatly reduced without affecting the therapeutic efficacy.

[0019] The effect of folic acid on GAR-transformylase inhibitors has been

demonstrated in standard tests commonly utilized to determine the antitumor activity and toxic effects of the GAR-transformylase inhibitors themselves. In one such test, mice are inoculated with the C3H strain of mammary adenocarcinoma by inserting a 2 mm by 2 mm section of tumor into the axillary region of the mice by trocar. In all experiments, lometrexol was administered intraperitoneally once a day for five consecutive days, starting on the day following tumor implantation. Ten animals were used at each dosage level. Antitumor activity was assessed on day ten by measuring the length and width of the tumor growth using vernier calipers.

[0020] When lometrexol was administered to infected mice which were maintained on a diet totally free of folic acid for two weeks prior to and during treatment, it exhibited moderate antitumor activity at very low doses, but also caused severe toxicity at a very low dose (measured as death of mice). These data are presented in Table 3 below.

[Table 3]

Antitumor activity and toxicity of lometrexol in C3H mice two weeks after feeding with folic acid free diet

| Lometrexol dose (mg/kg) | Antitumor activity (inhibiting rate (%)) | Toxicity (dead mice/total mice) |
|---|---|---|
| 0.0625 | 0 | 0/10 |
| 0.125 | 0 | 0/10 |
| 0.25 | 21 | 0/10 |
| 0.5 | 88 | 0/10 |
| 1.0 | 100 | 8/10 |

[0021] A test group of mice were maintained on a folic acid free diet for two weeks before treatment. Folic acid was then administered during the treatment by providing the animals drinking water containing 0.0003% (weight/volume) folic acid. This concentration translates to about 1.75 mg of folic acid per square meter of body surface per day, since the animals consume about 4 ml of water each day.

0.0003 g/100 ml × 4 ml/day = 0.000012 g/day = 0.012 mg/day

The average size of a mouse is 0.00687 $m^2$.

0.012 g/day × 1/0.00687 $m^2$ = 1.75 mg/$m^2$/day

For a human subject of about 1.73 $m^2$ in size, this translates to an adult human dosage of about 3.0 mg/day. The effect of the foregoing folate dosage on the activity and toxicity of lometrexol is shown in Table 4 below:

[Table 4]

Antitumor activity and toxicity of lometrexol in C3H mice that were fed with folic acid free diet for two weeks and then given water to which

0.0003% folic acid was added

| Lometrexol dose (mg/kg) | Antitumor activity (inhibiting rate (%)) | Toxicity (dead mice/total mice) |
|---|---|---|
| 0.125 | 13 | 0/10 |
| 0.25 | 26 | 0/10 |
| 0.5 | 48 | 0/10 |
| 1.0 | 97 | 0/10 |
| 2.0 | 98 | 0/10 |
| 4.0 | 99 | 4/10 |

As the foregoing results indicate, addition of the indicated level of folic acid to the diet of a subject receiving lometrexol results in excellent antitumor activity at low doses, with little or no toxic effects.

[0022] Larger doses of folic acid appear to have an even more dramatic effect on the antitumor activity and toxicity of the GAR-transformylase inhibitor. For example, when mice were maintained on a folate acid-free diet for two weeks before treatment with lometrexol, and then given water containing 0.003% (weight/volume) of folic acid (which translates to an adult human dose of about 30 mg/day), good antitumor activity of lometrexol was observed at higher dose levels. These results are shown in the following Table 5.

[Table 5]

Antitumor activity and toxicity of lometrexol in C3H mice that were fed with folic acid free diet for two weeks and then given water to which 0.003% folic acid was added

| Lometrexol dose (mg/kg) | Antitumor activity (inhibiting rate (%)) | Toxicity (dead mice/total mice) |
|---|---|---|
| 6.25 | 91 | 0/10 |
| 12.5 | 89 | 0/10 |
| 25 | 97 | 0/10 |
| 50 | 96 | 0/10 |

[0023] The foregoing data establish that for tumor bearing mice maintained on a folic acid free diet prior to and during treatment with lometrexol, the toxicity of lometrexol is very large, with 1 mg/kg/day being lethal to the majority of the mice, and lower antitumor activity is observed at non-toxic drug doses. Very low doses of folic acid (about 1 to 2 mg/day for an adult human) partially reversed drug toxicity and improved antitumor activity. Larger doses of folic acid (up to about 30 mg/day for an adult human) dramatically reduced lometrexol toxicity and markedly improved antitumor activity. Thus, the use of folic acid in combination with a GAR-transformylase inhibitor markedly reduces drug toxicity without adversely affecting

antitumor activity.

[0024] In a typical clinical evaluation involving cancer patients, all of whom have histologically or cytologically confirmed diagnosis of cancer, lometrexol is administered in combination with folic acid. Lometrexol is administered in four doses over a two-week period by rapid intravenous injection, followed by two weeks of non-therapy. Dosing is done on days 1, 4, 8, and 11 of any two-week period. Patients will have an initial course of therapy at a dose of 5 mg/$m^2$/dose, and depending upon the toxic effects observed in the initial course, their subsequent courses may be at the same dose, or may be escalated to 6 mg/$m^2$, or may be attenuated to 4 mg/$m^2$.

[0025] These patients will also receive orally 1 mg/day of folic acid, beginning the day before they are started on the first course of lometrexol, and continuing throughout their exposure to the drug. Such dosage of folic acid will be given once daily, generally in the morning hours.

[0026] In preparation for the foregoing clinical study, pilot studies in humans have established that folic acid given to patients receiving lometrexol has resulted in reduced side effects due to the lometrexol. Specifically, in one subject who had a nasalpharyngeal carcinoma, who was supplemented with folic acid at 0.5 to 1.0 mg/day, lometrexol was well tolerated for up to 12 months of therapy. Moreover, this patient showed no clinical evidence of disease after the 12 months of therapy. These data are consistent with the animal studies reported above.

B. Finding of Exhibit Ko 1 invention

(A) Claim 1 of the scope of claims of Exhibit Ko 1 describes the invention of toxicity reducing agent of antifolate such as GAR-transformylase inhibitor, the agent comprising an active ingredient of a folic acid binding protein binding agent such as folic acid, and the object is to reduce toxicity while maintaining therapeutic effects on antitumor antifolates ([Claim 1], paragraphs [0002] to [0004]).

The inventors of Exhibit Ko 1 invention have now discovered that the toxic effects of lometrexol and related GAR-transformylase inhibitors and other antifolate agents which bind to folate binding protein (FBP) can be significantly reduced by the presence of an FBP binding agent, without adversely affecting therapeutic efficacy. The invention described in Exhibit Ko 1 has solved the above problem on the basis of the discovery by administering antifolate in combination with folate binding protein binding agent ([Claim 1], paragraphs [0004] to [0006], [0012], and [0015] to [0018]).

An animal experiment using mice shows that the use of folic acid in combination with lometrexol markedly reduces drug toxicity without adversely

affecting antitumor activity (paragraphs [0021] to [0023]). In pilot studies in humans, folic acid given to patients receiving lometrexol has resulted in reduced side effects due to the lometrexol and has not shown any clinical sign of diseases, which is consistent with the above animal experiment (paragraphs [0024] to [0026]).

Further, Exhibit Ko 1 discloses administering folic acid or a salt or ester thereof to a human subject at a dose of about 0.5 mg/day to about 30 mg/day to diminish the toxic effects of antifolate of a GAR-transformylase inhibitor such as lometrexol (paragraph [0012]).

In view of the foregoing, Exhibit Ko 1 describes Exhibit Ko 1 invention described in the aforesaid No. 2, 3(1) as the trial decision found.

(B) Defendant alleges that it was only lometrexol for which antitumor activity and toxicity were actually studied in combination with folic acid in Exhibit Ko 1, and thus Exhibit Ko 1 invention should be recognized as an invention on lometrexol.

However, in Exhibit Ko 1, GAR-transformylase inhibitors (GARFT Inhibitors) are "compounds which effectively inhibit the physiological actions of the enzyme known as glycinamide ribonucleotide transformylase (GARFT)" (paragraph [0006]). MTA is a compound that inhibits physiological action of this GARFT (Exhibits Ko 2, 5, Ko 5-1, Ko 7). Further, it is recognized from each of the publicly known documents of the below-mentioned Exhibits Ko 2 to 4, 44 that it was known to a person ordinarily skilled in the art as of the priority date (including the case where the priority date of the Patent is the second priority date, the same shall apply hereinafter) that folic acid reduces the toxicity of MTA similarly and maintains antitumor activity. Therefore, it is recognized that a person ordinarily skilled in the art who read Exhibit Ko 1 as of the priority date would recognize that GAR-transformylase inhibitor (GARFT inhibitor) described therein also encompasses MTA. Consequently, in the finding of Exhibit Ko 1 invention, there is no reason to limit the GAR-transformylase inhibitor (GARFT inhibitor) to be lometrexol described in Exhibit Ko 1. Should lometrexol and MTA have a different mechanism to be taken into cells, this does not affect this determination.

Additionally, Defendant alleges that it was already known as of the priority date that the effectiveness of lometrexol was compromised when lometrexol and folic acid were used in combination, on the basis of Exhibit Ko 103 (Exhibit Otsu 3). This allegation is not acceptable in view of the description of Exhibits Ko 1, 42.

(2) Comparison between Invention 1 and Exhibit Ko 1 invention

According to the above (1) and the entire import of the oral argument, it is recognized that there are common features and different features of the aforesaid No.

2, 3(1)B as the trial decision found between Invention 1 and Exhibit Ko 1 invention. Further, Different Feature 1 is acknowledged as easily conceivable.

(3) Determination of Different Feature 2

Subsequently, a determination is made as to whether Different Feature 2 was easily conceivable

A. Publicly known facts and Common technical knowledge as of the priority date

(A) Publicly known documents on the combined use of MTA and folic acid, etc.

a. Exhibit Ko 2 (L. Hammond et al., "A PHASE I AND PHARMACOKINETIC (PK) STUDY OF THE MULTITARGETED ANTIFOL (MTA) LY231514 WITH FOLIC ACID (Meeting abstract)" American Society of Clinical Oncology, Meeting Abstract, No. 866, 1998)

"Abstract: Multitargeted antifolate (MTA; LY231514) is a novel antifolate having an inhibiting activity on a plurality of folic acid-dependent enzymes such as thymidylic acid producing enzyme, dihydrofolic acid reductase, and glycinamide ribonucleotide formyltransferase. An initial stage Phase I test has demonstrated major antitumor effects when injecting MTA for 10 minutes. However, the myelosuppression becomes a barrier and makes it impossible to gradually increase a dose beyond 500 to 600 mg/$m^2$. A preclinical test showed an improved therapeutic index of MTA by folic acid supplementation therapy. Thus in order to determine whether or not the toxicity action of MTA is reduced by folic acid supplementation therapy or it allows for significant gradual dose increase that exceeds a recommended dose of Phase II of MTA alone, the feasibility of administering 5 mg daily folic acid for five days starting two days before the administration of MTA was assessed in patients having minimum and extensive pretreatment histories. Until today, 21 cases of solid tumor patients were subjected to 55 courses on the basis of a regimen with doses of 600, 700, and 800 mg/$m^2$. Dose-dependent toxicities of neutropenia, anemia, and thrombocytopenia were observed, and patients having a history of a plurality of pretreatments were particularly severe. Toxicities of the other grade 1 to 2 were anthema, somnolentia, fatigue, edema of the leg, and decline of renal function developed by the decrease in creatinine clearance. Severe toxicity was developed in one case of patients who were taking non-steroid anti-inflammatory drug at a dose of 800 mg/$m^2$, but was diminished after the administration of leucovorin and thymidine. Partial response was recognized in one case of patients with metastatic colon cancer. Pharmacodynamics and vitamin (folic acid) metabolism profile were measured in the process of Cycle 1 and Cycle 3 treatment that were implemented at a dose of 600 to

800 mg/$m^2$. Although serum folic acid level is believed to be irrelevant to toxicities, a patient who developed severe toxicity at a dose of 800 mg/$m^2$ showed significantly increased homocysteine. So far, patients who have history of many or minimal pretreatments have shown tolerance with MTA at a dose of 600 mg/$m^2$ and 800 mg/$m^2$. The increase in amount was continued up to a dose of 700 and 900 mg/$m^2$. These results show that folic acid supplementation therapy allows for gradual dose increase of MTA."

b. Exhibit Ko 3 (John F. Worzalla et al., "Role of Folic Acid in Modulating the Toxicity and Efficacy of the Multitargeted Antifolate, LY231514", ANTICANCER RESEARCH 18, 1998)

page 3235, left column, lines 1 to 21

"Abstract. We studied the effects of folic acid on modulating the toxicity and antitumor efficacy of LY231514. ... Folic acid supplementation was demonstrated to preserve the antitumor activity of LY231514 while reducing toxicity. The combination of folic acid with LY231514 may provide a mechanism for enhanced clinical antitumor selectivity."

page 3238, right column, line 17 to page 3239, left column, line 2

"However, LFD grown animals supplemented with high levels of folic acid showed a decrease in fatality against LY231514 compared to animals grown with normal feedstuff. It is suggested that the good treatment with folic acid intake could achieve greater therapeutic effects. In these mice, the oral administration of folic acid drastically decreased the toxicity of LY231514, whereas the antitumor activity was maintained (The same shall apply to further higher doses.) (FIG. 2).

It is clarified that prior study multitargeted antifolate LY231514 has a unique biochemical and pharmacological profile. In Phase I and Phase II clinical tests, exciting antitumor activity was observed, including the response to colon cancer, breast cancer, non-small cell lung cancer, and pancreas cancer. A well advanced, larger scale clinical test of LY231514 is currently in progress. The combination of folic acid with LY231514 may provide a mechanism for enhanced clinical antitumor selectivity."

c. Exhibit Ko 4 (James J. Rusthoven et al., "Multitargeted Antifolate LY231514 as First-Line Chemotherapy for Patients With Advanced Non-Small-Cell Lung Cancer: A Phase II Study", Journal of Clinical Oncology, Volume 17, No. 4 (April), 1999)

page 1195, left column, lines 3 to 20

"MTA shows effects on many types of tumors. ... Earlier studies demonstrate the

possibility of improving therapeutic index while reducing toxicity by diet supplementation of folic acid."

d. Exhibit Ko 42

page 270, lines 19 to 34

"They concluded that patients were folic acid-deficient, and there was a growing need for folic acid in malignant disease patients. It is not surprising that these patients have different metabolism, pharmacodynamics, and toxicity of traditional antifolates from a person of normal folic acid level. Furthermore, dietary supplementation with folic acid may 'normalize' the dose response for achieving antitumor activity and reduce toxicity to normal tissues by restoring folate pools in tissues having low folate requirements, without meeting the high folate demands of rapidly dividing tumor cells.

The biochemical pathways that utilize folate cofactors also require adequate amounts of vitamins $B_{12}$ and $B_6$. Thus, the status of all three vitamins in patients may significantly influence the severity of toxicity observed during chemotherapy. R. Allen and his colleagues have established that measuring specific amino acid metabolites, especially homocysteine, N-methyl glycine, and others, from these metabolic pathways provides a more sensitive and reliable assessment of patient vitamin status (23). These surrogate indicators of functional folate status are more indicative of deficiencies and more responsive to dietary supplementation."

(B) Publicly known documents on MTA and homocysteine level

a. Exhibit Ko 5

page 8, left column, line 1 to page 9, left column, line 2

"Clinical measurement of functional folic acid status

The supplemental effect of folic acid for reducing toxicity of antifolates (in particular GARFT inhibitor) is definite; however, it has been always difficult to mutually correlate toxicity induced by antifolates with folic acid pretreatment level. One possible explanation is that folic acid level in measurement does not properly reflect the function of folic acid in proliferating cells. In addition to the pathways discussed so far, folic acid is also involved in cellular methylation reactions by virtue of the efficacy of its role in methionine synthesis. $CH_2FH_4$ can be reduced to 5-methyltetrahydrofolate (FIG. 1). This is a substrate for the enzyme methionine synthase, which uses methyl group to convert homocysteine to methionine. Methionine in turn takes part in intracellular methylation regenerating homocysteine. Methionine synthase is B12-dependent but also uses 5-methyltetrahydrofolate as the co-substrate. Therefore, any functional deficiency of B12 or folic acid results in a decreased flow through methionine synthase and increased plasma level of

homocysteine 16 (FIG. 8). The measurement of pretreatment plasma homocysteine has proved to be a sensitive way of predicting the toxicity of MTA."

page 9, FIG. 8

"

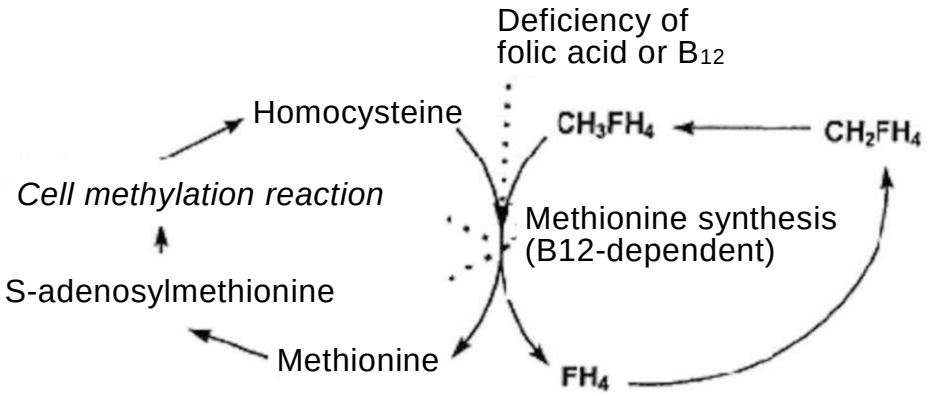


FIG. 8. Role of 5-methyltetrahydrofolic acid: The functional decrease in folic acid results in elevated homocysteine level in plasma."

b. Exhibit Ko 6

page 127, left column, lines 12 to 18

"Conclusions: Toxicities developed by a treatment with MTA are considered to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels (≥10 μM) showed a strong correlation with severe hematologic toxicity and nonhematologic toxicities following treatment with MTA. It has been clarified that homocysteine level is a better predictor of toxicity compared to albumin level."

c. Exhibit Ko 7 (hereinafter referred to as "Niyikiza document")

page 558a, the right column, lines 2 to 33

"LY231514 (MTA); Relationship between vitamin metabolism profile and toxicity, C. Niyikiza, *J. Walling, D. Thornton, D Seitz, and R. Allen. Eli Lilly and Company Indianapolis, IN, and Univ. of Colorado Health Science Center, Denver, CO*

LY231514 (MTA) is a new generation multitargeted antifolate having an inhibiting activity on thymidylic acid producing enzyme, dihydrofolic acid reductase, and glycinamide ribonucleotide formyltransferase. In the Phase II test, vitamin metabolites were measured for 118 cases out of 246 cases in total that were subjected to treatment with MTA (600 mg/$m^2$ was intravenously infused for 10 minutes every 21 days). Earlier studies using the other antifolates suggested the possibility of the nutrition status being associated with risk of developing severe toxicity, and thus each level of vitamin metabolites of homocysteine, cystathionine, and methylmalonic acid was measured once for baseline and each cycle. Data were subjected to multivariate

statistical analysis, and what kinds of factors in a series of predetermined predictors (creatinine clearance, albumin level, liver enzyme level, and vitamin metabolites) are associated with toxicity were investigated There was a strong correlation between homocysteine level at baseline and the following toxicity development observed at any timing during a test period. It is Grade 4 neutropenia (57 cases, $P<0.0001$), Grade 4 thrombocytopenia (13 cases, $P<0.0001$), Grade 3 or 4 mucositis (8 cases, $P<0.0003$), and Grade 3 or 4 diarrhea (8 cases, $P<0.004$) on the basis of CTC. Regarding cystathionine level, the correlation with hematological toxicity or mucositis was not shown, but a moderate correlation was observed with fatigue ($P<0.04$). The maximum level of cystathionine doubled baseline value during MTA therapy period. There is no correlation between toxicity (CTC grade defined above) and the remaining predictor. Toxicity was observed for all patients with a homocysteine level beyond 10 μM. Further, there was a time-course correlation between homocysteine level, CTC grade 4 neutropenia, thrombocytopenia, and CTC grade 3 or 4 mucositis only in the first two cycles of therapy regimen. During a period of MTA therapy, no variation was observed from a baseline of the maximum homocysteine level."

d. Exhibit Ko 44 (Alex A. Adjei, "A review of the pharmacology and clinical activity of new chemotherapy agents for the treatment of colorectal cancer", 1999)
page 270, left column, line 12 from the bottom to line 2 from the bottom
"Cumulative results from several clinical trials indicate that the folate status of patients is a sensitive predictor of toxicity from MTA. The most sensitive indicator of folate status appears to be serum homocysteine. Patients with serum homocysteine levels above a threshold concentration of 10 μM are at significant risk of developing severe myelosuppression, mucositis, or diarrhea [52] (court decision's note:[52] indicates Niyikiza document.). The dose of MTA has been successfully escalated up to 1000 mg $m^{-2}$ every 3 weeks with folate supplementation, which may not adversely affect the antitumor activity of MTA [53]."

(C) Common general knowledge about folic acid metabolism and the action, etc. of vitamin $B_{12}$ associated therewith

Regarding folic acid metabolism and the action, etc. of vitamin $B_{12}$ associated therewith, there was the following common general knowledge.

In addition, Defendant alleges that the detailed content described in Exhibit Ko 115 did not fall within the common general knowledge of a person ordinarily skilled in the art who worked on cancer chemotherapy. However, in view of the fact that the Invention is an invention related to an anticancer agent of antifolate or a method

for administering the antifolate, it is hardly believed that the details of folic acid metabolism in the human body as described in Exhibit Ko 115 were not a common general knowledge of a person ordinarily skilled in the art. Defendant's allegation is not acceptable.

a. Folic acid metabolism in cells of human body (Exhibits Ko 5, 10 to 16, 19, 69, 115, Exhibit Otsu 21, the entire import of the oral argument)

Folic acid is reduced from dihydrofolate to tetrahydrofolate by causing folic acid taken from outside the body to be catalyzed by dihydrofolate reductase as shown in the following scheme, thereby being involved with both nucleotide biosynthetic reaction associated with DNA synthesis and methylation reaction involved with methionine synthesis.

In nucleotide biosynthesis reaction, tetrahydrofolic acid is recycled by causing dihydrofolic acid produced by methylene group leaving of 5, 10-methylenetetrahydrofolic acid in the synthesis of thymidylic acid to be catalyzed by dihydrofolate reductase to produce tetrahydrofolic acid, and is also recycled by use of formyl group of 10-formyltetrahydrofolic acid in the synthesis of purine base.

In methylation reaction, 5-methyltetrahydrofolic acid reduced from 5,10-methylenetetrahydrofolic acid synthesized from tetrahydrofolic acid is used as an assisting substrate in vitamin $B_{12}$-dependent methionine synthesis to be involved with methionine synthesis from homocysteine to be recycled into tetrahydrofolic acid. Therefore, should either of folic acid or vitamin $B_{12}$ be deficient, homocysteine level is elevated.

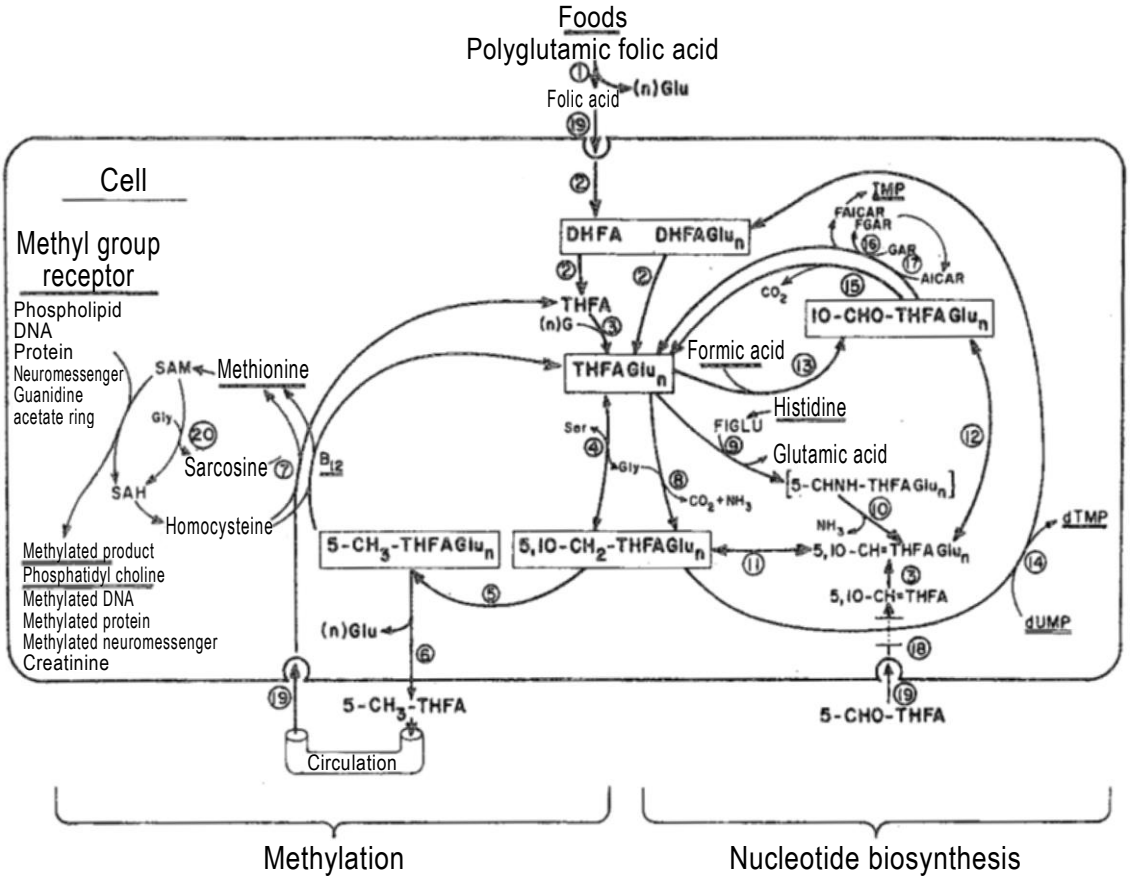


**FIG. 2 Enzyme and reaction of folic acid metabolism**

① γ-glutamyl hydrolase (brush border?) (EC3.4.22.12), ② Dihydrofolate reductase (EC1.5.1.3), ③ Folylpolyglutamate acid synthase (EC6.3.2.17), ④ Serine hydroxymethyl transferase (EC2.1.2.1), ⑤ Methylene tetrahydrofolate reductase (EC1.7.99.5), ⑥ γ-glutamyl hydrolase (lysosome?) (EC3.4.22.12), ⑦ Cobalamin-dependent methionine synthase (EC2.1.1.13), ⑧ Glycine-cleaving enzymes (EC1.4.4.2; 2.1.2.10), ⑨ Formiminoglutamate transferase (LEC2.1.2.5), ⑩ Formiminotetrahydrofolate cyclodeaminase (EC4.3.1.4), ⑪ Methylene tetrahydrofolate dehydrogenase (EC1.5.1.5), ⑫ Methenyl tetrahydrofolate cyclohydrolase (EC3.5.4.9), ⑬ Formyl tetrahydrofolate synthase (EC6.3.4.3), ⑭ Thymidylate synthase (EC2.1.1.45), ⑮ Formyl tetrahydrofolate dehydrogenase (EC1.5.1.6), ⑯ Phosphoribosyl glycinamide (GAR) formyl transferase (EC2.1.2.2), ⑰ Phosphoribosyl aminoimidazole carboxamide (AICAR) formyl transferase (EC2.1.2.3), ⑱ 5-formyltetrahydrofolate cyclo-ligase (EC6.3.3.2), ⑲ Folic acid/MTX transportation system, and ⑳ Glycine methyl transferase (EC2.1.1.20).

b. Correlation between methylmalonic acid level and vitamin $B_{12}$ (Exhibit Ko 14, the entire import of the oral argument)

As in the above item a, homocysteine level varies depending on the status of folic acid and vitamin $B_{12}$, whereas methylmalonic acid level increases due to vitamin $B_{12}$ (cobalamin) deficiency, and thus is a selective indicator for vitamin $B_{12}$.

c. Decrease in homocysteine level (Exhibits Ko 8 to 16, the entire import of the oral argument)

Homocysteine level is elevated in a case of folic acid and/or vitamin $B_{12}$ deficiency, whereas the combined use of folic acid and vitamin $B_{12}$ may securely decrease homocysteine level compared to the case of simple administration of folic acid only.

As of the priority date, it was supposed that 0.5 to 5 mg of folic acid and about 0.5 mg of vitamin $B_{12}$ supplementation in European could expect the decrease in blood homocysteine level by one-fourth to one-third.

B. In view of the content of Exhibit Ko 1 of the aforesaid (1) and the publicly known documents and the common general knowledge as of the priority date as found in the above A, a consideration is given as to whether Different Feature 2 is easily conceivable.

(A) As found in the aforesaid (1), Exhibit Ko 1 describes the object to reduce toxicity of a GAR-transformylase inhibitor, while maintaining the therapeutic effects thereof. Exhibit Ko 1 allegedly solves the problem by administering folic acid in combination with a GAR-transformylase inhibitor. As for the problem, there is neither motivation nor suggestion in Exhibit Ko 1 to positively apply an additional active ingredient such as vitamin $B_{12}$.

In addition to this, it can be seen from Exhibits Ko 2 to 4, 44 of the above A(A)(B) that there are a plurality of the publicly known documents that mention the combined use of MTA and folic acid for the purpose of reducing toxicity while maintaining antitumor activity of MTA before the priority date, it is recognized that it was a common general knowledge to administer MTA in combination with folic acid for that purpose. None of publicly known documents points out that merely folic acid supplementation is insufficient for the above purpose, or the necessity to administer the other active ingredient in addition to the folic acid supplementation.

(B) As per the above A(B)(C), it was known as of the priority date that [i] the toxicity development of MTA is highly predicted when homocysteine level at baseline is 10 μM or more, [ii] homocysteine level increases if folic acid and/or vitamin $B_{12}$ is

insufficient, and [iii] when folic acid and vitamin $B_{12}$ are administered in combination, homocysteine level can be decreased more securely as compared to the case of single dose of folic acid; however, it can be seen from the following a, b that these facts would not motivate a person ordinarily skilled in the art to combine the administration of vitamin $B_{12}$ with Exhibit Ko 1 invention.

a. What is pointed out by each publicly known document of the above A(B) is only that homocysteine level at baseline was a predictor that allowed us expect the development of MTA toxicity as of the priority date. It cannot be read that "the decrease in homocysteine level at baseline suppresses the development of MTA toxicity" as Plaintiff alleges. In this regard, Plaintiff alleges that there is a causal relationship between "homocysteine level at baseline" and "toxicity after MTA administration". If there were a simple proportional relationship between homocysteine level at baseline and the development of MTA toxicity, Plaintiff's allegation might apply; however, it is not recognized from evidences that it was known as of the priority date that there is a simple proportion correlation (rather, Exhibit Ko 115 [page 212, left column, lines 5 to 6] discloses that there is a nonlinear inverse correlation between folic acid functioned status and plasma homocysteine level). Therefore, it cannot obviously be deduced from "high homocysteine level at baseline was a predictor that allows us expect the development of MTA toxicity" that "keeping the decrease in homocysteine level at baseline suppresses the development of MTA toxicity". The above Plaintiff's allegation is groundless.

Further, when it comes to the fact that "decreasing homocysteine level at baseline maintains antitumor activity", each of the above publicly known documents is totally silent, except that Exhibit Ko 44 describes that the toxicity is reduced while maintaining antitumor activity by folic acid supplementation. Thus this point cannot be acknowledged to be a common general knowledge.

Consequently, it cannot be recognized as of the priority date as a common general knowledge that "decreasing homocysteine level at baseline suppresses the development of toxicity and maintains antitumor activity" as Plaintiff alleges. Thus it cannot be said from the point that there is a motivation.

b. Differing from homocysteine level elevated by the deficiency of folic acid or vitamin $B_{12}$, methylmalonic acid level is elevated by the deficiency of vitamin $B_{12}$ (the above A(C)b). As per the above A(B), the Niyikiza document pointed out as of the priority date that there was a correlation between the homocysteine level at baseline and the development of toxicity; however, there was no correlation between the status of methylmalonic acid level and the development of toxicity. Thus, it is

deduced from this that a person ordinarily skilled in the art would be guided to supplement folic acid with a thought that there is no correlation between the status of vitamin $B_{12}$ and the development of toxicity of patients, but rather the deficiency of folic acid is associated with the increase in homocysteine level at baseline or the development of toxicity. Currently, as per the above A(B)d, Exhibit Ko 44 citing the Niyikiza document in note 52 only mentions about folic acid supplementation, while pointing out that 10 μM homocysteine level at baseline is a threshold value of the development of toxicity, and recognizes that homocysteine level is a barometer of folic acid status.

Further, the combined use of folic acid and vitamin $B_{12}$ promotes methylation for producing methionine at the left side of figure of the above A(C)a, and facilitates the recycling of tetrahydrofolate. It can thus be said that the administration of vitamin $B_{12}$ serves for the further improvement of the functional state of folic acid compared to the single dose of folic acid; however, it is unclear from the evidence as to the extent to which such promotion of recycling of tetrahydrofolate might affect the functional state of folic acid. It cannot be acknowledged that a person ordinarily skilled in the art as of the priority date could have recognized that it was insufficient to supplement folic acid from the outside, but necessary to supplement even vitamin $B_{12}$ in order to normalize the functional state of folic acid in cancer patients.

Consequently, even if a person ordinarily skilled in the art should think that it was necessary to decrease homocysteine level at baseline below 10 μM for reducing toxicity risk of MTA, a person ordinarily skilled in the art would not be motivated to add vitamin $B_{12}$.

(C) Plaintiff alleges that unmet medical needs against disease for which no therapy has yet been discovered would motivate addition of another active ingredient, seeking further improved effects.

As considered in the above (A)(B), however, it cannot be acknowledged that a person ordinarily skilled in the art had recognized the insufficiency of the pretreatment only with folic acid for the purpose of reducing toxicity while maintaining antitumor activity of antifolates. Thus, even in the presence of unmet medical needs as Plaintiff alleges, it cannot be directly inferred from the fact that a person ordinarily skilled in the art recognizes the necessity of further improvement of Exhibit Ko 1 invention for the above purpose.

Further, even if it should be motivated by unmet medical needs to improve Exhibit Ko 1 invention for the above purpose, in view of the consideration of the above B(B), it cannot be motivated to further use vitamin $B_{12}$ in combination.

Plaintiff's allegation is not acceptable from that viewpoint.

In addition, should Exhibit Ko 2 describes neither motivation nor suggestion in its nature, it would not affect the above determination.

C. Inventions 2 to 5 directly or indirectly depend from the Invention 1. Inventions 6 and 7 have Different Feature 2 from Exhibit Ko 1 invention, similar to Invention 1. As is considered so far, Different Feature 2 is not easily conceivable. Thus it cannot be said that Inventions 2 to 7 are easily conceivable.

D. Therefore, Reason 1 for rescission presented by Plaintiff is groundless without the determination of the remaining points.

3. Reason 2 for rescission (error in the finding and the determination of lack of novelty)

(1) Factual relationship

Regarding the present clinical test etc., the following facts are recognized:

A. Clinical test

(A) The present clinical test was an unblind Phase II clinical test for an anticancer agent of MTA conducted for patients with malignant pleural mesothelioma (in the clinical test, there are limited number of patients for evaluating safety and effectiveness of drugs [investigational agent], pharmacodynamics, and the optimal administration method and dose period of drugs), and was conducted in 10 facilities of four countries of Germany, Italy, England, and the United States, and the test period was one year and ten and one-half months (September 1, 1999 to July 14, 2001) (Exhibits Ko 21 to 23 [as for Exhibits Ko 21, 22, translation Exhibits Ko 21-1, Ko 22-1 are included, the same shall apply hereinafter], Exhibits 54, 133, the entire import of the oral argument).

(B) In the present clinical test 64 patients participated in total, in which patients with no vitamin administration were initially included. For improved safety of patients, protocol was amended just before the end of first phase, and after December 10, 1999, folic acid and vitamin $B_{12}$ were administered for all the patients who were subjected to a clinical test treatment at that time (Exhibits Ko 21 to 23, 133, the entire import of the oral argument).

Additionally, the present clinical test included 43 patients with vitamin dose and 21 patients without vitamin dose. The latter did not receive vitamin dose initially, but included patients who received vitamin dose after December 10, 1999 (Exhibits Ko 21, 22).

(C) The major object of the clinical test was to clarify the tumor response rate of patients with malignant pleural mesothelioma who received the MTA dose. A

secondary object involves implementing quantitative and qualitative characteristics analysis for the toxicity of MTA which was administered to patients with malignant pleural mesothelioma every 21 days (Exhibit Ko 22).

(D) MTA therapy supplementing folic acid and vitamin $B_{12}$ implemented after December 10, 1999 in the present clinical test is set forth as below (Exhibits Ko 21, 22):

- For all registered patients, 500 mg/$m^2$ MTA was administered by intravenous infusion for 10 minutes at Day 1 in one course of 21 days.
- For primary prophylaxis of anthema, for all the patients registered in the present clinical test, 4 mg dexamethasone (or corticosteroid equivalent to 4 mg dexamethasone) was orally administered twice daily a day before, the current day, and the day after MTA administration of each time.
- About one to two weeks before the initial dose of MTA, the oral administration of 350 μg to 1000 μg folic acid for consecutive days was started, and continued to one to two week after the discontinuation of administration of MTA to patients.
- About one to two weeks before the initial dose of MTA, 1000 μg vitamin $B_{12}$ infusion was intramuscularly administered, and was continued about every 9 weeks.

(E) In the present clinical test, Investigator had a duty of confidentiality for at least 10 years after the completion of clinical test with regard to all information received and knowledge obtained by him/herself in the course of the clinical test. Unless it is the case where Investigator is required to share information with patients, by laws, regulations, etc. it was specified that no information shall be used for a purpose other than specified by the agreement. In a case that Investigator is requested by other individuals or groups to disclose data, he/she shall notify the company immediately (Exhibit Ko 134, the entire import of the oral argument).

B. Regulation on clinical test

(A) The development of pharmaceutical products generally follows steps of confirming the effectiveness and safety of novel substance, which can be a candidate pharmaceutical product in non-clinical test in which animals such as mice or rats are used, and then conducting clinical tests of Phase I to Phase III on humans to confirm the effectiveness, safety, quality, etc., and filing an application for manufacturing approval with a pharmaceutical product regulation authority (Exhibit Ko 54, the entire import of the oral argument).

(B) For clinical testing, a standard called GCP (good clinical practice) is established. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which was established by

six industry groups and each drug regulatory authority of Japan, the United States, and Europe in 1990, prepared a final draft of guideline regarding GCP titled "ICH HARMONISED TRIPARTITE GUIDELINE FOR GOOD CLINICAL PRACTICE E6 (R1)" (ICH-GCP guideline) on June 1996 to advise each drug regulatory authority of Japan, the United States, and Europe to approve the guideline. Accordingly, in Japan, "Ministerial ordinance regarding the standard of the implementation of the clinical test of pharmaceutical products" was published on March 27, 1997 in accordance with the ICH-GCP guideline and was implemented from April 1 of the same year (Exhibits Ko 36, Ko 36-1, Ko 37, 54, the entire import of the oral argument).

The present clinical test was also conducted in compliance with the above ICH-GCP guideline (Exhibit Ko 134, the entire import of the oral argument).

(C) The ICH-GCP guideline has the following provision (Exhibit Ko 36, the entire import of the oral argument).

2.3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

4.8.2. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.6. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.10. Both the informed consent discussion and the written informed consent form, and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research
(b) Object of clinical test
(c) The trial treatment(s) and the probability for random assignment to each treatment.
(d) The trial procedures to be followed, including all invasive procedures.
...
(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
5. 12. 1. Information on Investigational Product(s)
When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

(2) Determination

A. Determining on the basis of the aforesaid (1), as per the aforesaid (1)A(B) to (D), the present clinical test was conducted for MTA as an anticancer agent, and it is recognized that the dose amounts, the timing and the route of administration of MTA, folic acid, and vitamin $B_{12}$ in MTA therapy used in the present clinical test, in which folic acid and vitamin $B_{12}$ are administered, are encompassed in those of Inventions 1 to 7.

B. As per the aforesaid (1)B(B), the present clinical test was conducted in compliance with ICH-GCP guideline. As per the aforesaid (1)B(C), ICH-GCP guideline 4.8.10 specifies that the written agreement of informed consent must include "objective of the clinical test", "details of treatment in the clinical test", "procedure of the clinical test", and "reasonably expected benefit". According to the above provision of ICH-GCP guideline, it can be assumed that there was an offer of information to patients subjected to vitamin supplementation in the present clinical test to the extent that an anticancer agent to be administered is MTA, and folic acid and vitamin $B_{12}$ were administered in combination; however, the ICH-GCP guideline fails to definitely specify "objective of the clinical test", "details of treatment in the clinical test", "procedure of the clinical test", and "reasonably expected benefit" to be described in the written agreement, etc., or to what extent information should be disclosed. It is unclear from the evidences as to what laws, regulations, and practices were in effect at that time in foreign countries where the present clinical test was implemented. Consequently, it cannot be acknowledged that information such as specific dose amounts, the timing and the route of administration of MTA, folic acid, and vitamin $B_{12}$, and the route or information of "reducing toxicity associated with

MTA administration while maintaining antitumor activity" were described in the written agreement, etc. of informed consent, going further from information reasonably deducible as being disclosed as above.

Further, ICH-GCP guideline 4.8.7 specifies that Investigator should answer questions from patients and their legally accepted representative (hereinafter collectively referred to as "patients and others") until patients and others are satisfied in getting agreement with patients; however, the provision of "should answer questions ... until patients and others are satisfied" is too abstract to find from the evidences that there were circumstances where all information including information such as specific dose amounts, the timing and the route of administration of MTA, folic acid, and vitamin $B_{12}$, or information of "reducing toxicity associated with MTA administration while maintaining antitumor activity" were ready to be provided from Investigator to patients and others upon request from patients and others, let alone find that all of this information was actually provided from Investigator upon request from patients and others.

In addition, there is no fact to find that patients and others knew or could have known of the Invention in the present clinical test.

Therefore, it cannot be acknowledged that the Invention was "publicly known" or "publicly worked" in the present clinical test.

C. Plaintiff alleges that information about specific dose amounts, the timing and the route of administration of MTA, folic acid, and vitamin $B_{12}$ was provided or could have been provided in the present clinical test in view of [i] ICH-GCP guideline and the declaration of A (Exhibit Ko 23), the written agreement of the clinical test of National Cancer Research Center (Exhibit Ko 38), and the written opinion of Professor B (Exhibit Ko 56).

However, it cannot be directly deduced from the ICH-GCP guideline that the Invention was a publicly known invention or a publicly worked invention, as considered in the above B.

Regarding the declaration statement of A (Exhibit Ko 23), it describes that A explained to patients the details of the present clinical test, the administration of vitamin $B_{12}$ and folic acid, and that it reduces the toxicity of MTA. In view of the fact that C, who was involved the present clinical test, stated in the declaration (Exhibit Ko 133) that there was no patient subjected to vitamin administration in patients to whom A attended, it cannot be acknowledged that the above description of the declaration statement of A (Exhibit Ko 23) that A explained to patients the details of the present clinical test, the administration of vitamin $B_{12}$ and folic acid, and that it

is intended for reducing the toxicity of MTA, is a statement about what was experienced by A as a reality by itself, and thus the declaration is not reliable. Further, it is difficult to believe that the declaration concretely states what kind of information was provided or could have been provided for patients and others. Thus it cannot be acknowledged from the declaration that information such as specific dose amounts, the timing and the route of administration of MTA, folic acid, and vitamin $B_{12}$, or information of "reducing toxicity associated with MTA administration while maintaining antitumor activity" had been conveyed or could have been conveyed to patients upon request from patients and others.

Regarding the written agreement (Exhibit Ko 38) used in the National Cancer Research Center, it only clarifies the current practice in Japan. It cannot be deduced from the agreement how patients were treated at the time of implementing the present clinical test in accordance with ICH-GCP guideline in foreign countries where the present clinical test was conducted. The same shall apply to the written opinion by Professor B.

Therefore, the above argument presented by Plaintiff is not acceptable, and the aforesaid finding B is not affected.

D. For the above reasons, Reason 2 for rescission presented by Plaintiff is groundless without the determination of the remaining points.

No. 5 Conclusion

Therefore, the Plaintiff's claim is groundless and thus shall be dismissed, and the court renders as in the formal adjudication.

Intellectual Property High Court, Second Division

Presiding Judge MORI Yoshiyuki
Judge MANABE Mihoko
Judge KUMAGAI Daisuke