LIFE SCIENCES INTELLECTUAL PROPERTY REVIEW

Regimen patents in Japan: LCM failures and successes

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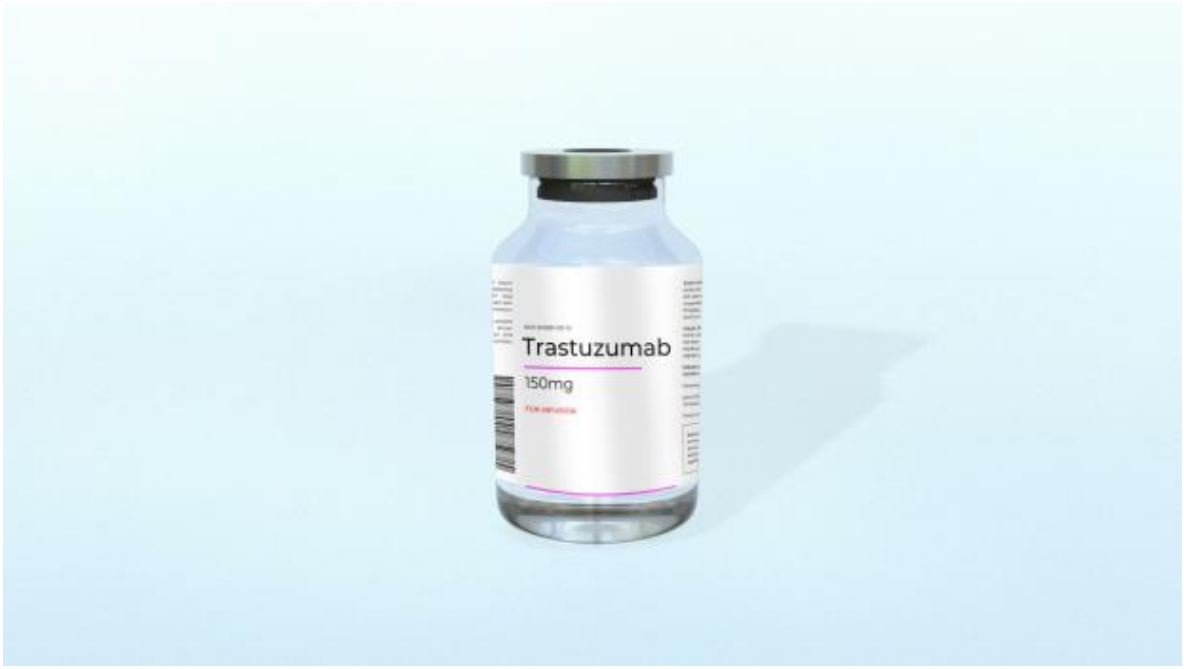

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Examining a series of case studies, Takanori Abe of Abe & Partners provides an overview of lifecycle management failures and successes in regimen patents.

Regimen patenting is part of the lifecycle management (LCM) strategy of originator companies. The following is an overview of LCM failures and successes in regimen patents.

LCM failures

1. **Rituxan**

Patent

Claim 1 of Patent 1

“A pharmaceutical composition for use in combination with a chemotherapy regimen for human patient in a treatment of low grade/follicular non-Hodgkin’s lymphoma (NHL), including rituximab, wherein a

therapeutically effective amount of the pharmaceutical composition is administered to the patient during a chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)."

Claim 1 of Patent 2

"A pharmaceutical composition for use in combination with a chemotherapy regimen for human patient in a treatment of low grade/follicular non-Hodgkin's lymphoma (NHL), including rituximab, wherein a therapeutically effective amount of the pharmaceutical composition is administered to the patient during the chemotherapy, and the chemotherapy is CVP therapy."

Judgment of May 29, 2019, Tokyo District Court

The wording "during" in Element 1B was altered from "at the same time" in the divisional application of Patent 1. This "at the same time" includes a mode in which each pharmaceutical contained in the CHOP therapy and rituximab are alternately administered, meaning administration during rest periods is included, and this mode is described in Exhibit 38. The wording "during" was introduced in an amendment to overcome the reason for refusal.

Therefore, "during a chemotherapy with (CHOP)"of the Element 1B does not include administration during rest periods of each pharmaceutical of the CHOP therapy. Instead, it means the "administration period of each pharmaceutical of CHOP therapy" during the entire treatment cycle. The detailed description of the invention of the specifications of Patents 1 and 3 does not describe or suggest the use of Inventions 1 and 3, therefore, Patents 1 and 3 violate article 36(6)(i) of the Patent Act.

As of the filing date of the original application, the CVP therapy and the COP therapy were distinguished by the administration timing of cyclophosphamide. In CVP therapy cyclophosphamide ais administered from Day 1 through to Day 5 whereas in CPO therapy only on Day 1, and such a distinction was common general knowledge.

Hence the reference to CVP in Element 2B means that cyclophosphamide is administered from Day 1 through to Day 5, and doesn't include those in which cyclophosphamide is administered only on Day 1. The R-CVP regimen described in the label of Sandoz and Kyowa Kirin's preparation is recognised as a regimen to administer cyclophosphamide only on Day 1, therefore, Sandoz and Kyowa Kirin's preparation does not meet the criteria for CVP of the Element 2B.

2. **Herceptin: Neoadjuvant chemotherapy**

(1) Patent

Claim 1

"A pharmaceutical comprising a therapeutically effective amount of humanised 4D5 anti-ErbB2 antibody for the treatment of a human patient diagnosed with breast tumour where ErbB2 protein is expressed, the treatment comprising implementing the following steps in the following order of: (a) treating the patient with the pharmaceutical; (b) surgically removing the tumour; and (c) treating the patient with the pharmaceutical or a chemotherapeutic agent."

(2) Judgment of October 22, 2018, IP High Court

It was common general knowledge that in operable breast cancer, it was a common therapy for operable breast cancer to implement neoadjuvant chemotherapy, then surgically remove tumours, and then further implement adjuvant chemotherapy.

Further, Exhibit 2, titled "future trend of neoadjuvant therapy for breast cancer" discloses that "The role of these new strategies in combination with primary chemotherapy should be evaluated by early-stage breast cancer patients" right after introducing a clinical trial where anti-HER2 antibody and doxorubicin or cyclophosphamide are co-administered to metastatic breast cancer patients.

Taking the above into account, it is recognised that a skilled person who read Exhibit 1 could have easily conceived of co-administering a pharmaceutical of Exhibit 1 invention with a chemotherapeutic agent before surgery, conducting a surgery, and further coadministering the pharmaceutical of Exhibit 1 invention with the chemotherapeutic agent after surgery for the treatment of operable breast cancer that overexpresses HER2 protein.

3. **Herceptin: method B**

(1) Patent

Claim 6

“A pharmaceutical composition for the treatment of breast cancer characterised by overexpression of HER2, the pharmaceutical composition containing an anti-ErbB2 antibody huMab4D5-8, the treatment comprising administering to the patient by intravenous injection an initial administration of 8 mg/kg of the antibody followed by two or more subsequent administrations of 6 mg/kg of the antibody, wherein the subsequent administrations are separated in time from each other by at least three weeks.”

(2) Judgment of October 11, 2018, IP High Court

A skilled person would have had common general knowledge as of the priority date that a larger dosage might possibly extend the administration interval in common pharmaceutical products comprising a therapeutic agent for breast cancer, that dosage and administration intervals were adjusted for observation of efficacy and side effects in the development of pharmaceutical composition, and that the extension of the administration interval might decrease the cost of hospital visits, as well as the pain and suffering in administration for patients, and therefore would be preferable from a viewpoint of cost efficiency and convenience.

A skilled person who has common general knowledge would easily try not only to administer the antibody in a 4/2/1 dosage regimen as in cited invention 2-1, but also to adjust the dosage and the administration interval of the antibody while observing efficacy and side effects, and adjust the administration period of the antibody to 3 weeks in accordance with the administration period of chemotherapeutic agent to be combined from a viewpoint of cost efficiency and convenience, and furthermore, to increase the dosage of the antibody as necessary within a range up to 8 mg/kg or so. Further, a skilled person could have easily conceived of administering the antibody in an 8/6/3 dosage regimen with an exercise of ordinary inventive ability.

The declaration of Doctor A (Exhibit 8) disclosed that oncologists would not be motivated to administer the antibody in an 8/6/3 dosage regimen, since experimenting with an untested dosage regimen might put

patients' lives at risk; however, the lack of motivation in clinicians to clinically try a new dosage and administration regimen of a pharmaceutical does not negate the motivation to try the development of new dosage and administration regimen *per se*.

4. **Taxol**

(1) Patent

Claim 1

“A pharmaceutical containing Taxol for treatment of patients suffering from solid cancer, leukaemia, or ovarian cancer and who have been premedicated to reduce or minimise hypersensitivity reactions and who pose concerns of hematologic toxicity accompanying treatment with Taxol, said pharmaceutical being packaged for parenteral administration such that about 135 mg/m2 - about 275 mg/m2 Taxol is administered over a period of about three hours.”

Claim 2

“The pharmaceutical of claim 1, wherein the patients have solid tumour or leukaemia and who have been premedicated to reduce or minimise hypersensitivity reactions, wherein the dose of Taxol is greater than 175 mg/m2 and less than about 275 mg/m2.”

Claim 3

“The pharmaceutical of claim 1, wherein the patients have ovarian cancer and who have been premedicated to reduce or minimise hypersensitivity reactions, wherein the dose of Taxol is greater than 175 mg/m2 and less than about 275 mg/m2.”

(2) Judgment of March 1, 2007, IP High Court

Since there is no statement in the detailed description of the invention to support the efficacy and safety of a 3-hour Taxol administration exceeding 175 mg/m2, patented inventions 2 and 3 do not include specific data that can confirm their efficacy and safety in the detailed description of the invention. There is also no statement supporting efficacy or safety in patients with solid cancers other than ovarian cancer or leukaemia. Therefore, patented invention 2 does not include specific data that can confirm its efficacy and safety in the detailed description of the invention.

The clinical trial protocols described in Exhibits 1 to 4 are the clinical trial protocols for the patented invention 1, and Exhibits 1 to 4 state that "Taxol should be parenterally administered to patients with ovarian cancer at administration of 175 mg/m2 and 135 mg/m2 as an anticancer pharmaceutical over 3 hours", therefore, the patented invention 1 is identical to the invention described in Exhibits 1 to 4. Exhibits 19 to 21 submitted by BMS (expert opinions) only state that a doctor cannot immediately prescribe Taxol in a clinical place as a medical practice. This does not mean that a mode satisfying the elements of the invention 1 is not described in Exhibits 1 to 4.

LCM successes

1. **Herceptin: Infringement lawsuit**

(1) Patent

Claim 1

“(i) A container containing a pharmaceutical composition for the treatment of breast cancer characterised by overexpression of HER 2, the pharmaceutical composition containing an anti-ErbB2 antibody huMab4D5-8, the treatment comprising administering to the patient by intravenous injection an initial administration of 8mg/kg of the antibody followed by two or more subsequent administrations of 6mg/kg of the antibody, wherein the subsequent administrations are separated in time from each other by at least three weeks and (ii) a package comprising a package insert associated with the container.”

(2) Chugai’s press release, the Pharmaceuticals and Medical Devices Agency (PMDA)

Chugai issued a press release saying that it confirmed that the product developed by Nippon Kayaku received a marketing approval for the indication of “unresectable advanced or recurrent gastric cancer where overexpression of HER2 was observed.” As a result, it judged that the initial purpose of the lawsuit was achieved, and took the procedure for waiver off its claims.

In the minutes for the Pharmaceutical Affairs and Food Sanitation Council (PAFSC) Second Committee on Drugs, the PMDA stated, “I assume that since the associated company of Chugai possesses the patent related to breast cancer, the timing of obtaining effectiveness and efficacy for breast cancer will vary depending on whether or not there is a conflict with the patent.” The above argument shows that the existence of a use patent had an impact on the approval in relation to specific effectiveness and efficacy.

2. **Alimta**

(1) Patent

Claim 1

“A pharmaceutical for inhibiting tumour growth in humans, comprising pemetrexed disodium used with folic acid and vitamin B12, the pharmaceutical administered according to the following regimen: a. administering an effective amount of the pharmaceutical; b. administering 0.3 mg to 5 mg of folic acid prior to administration of the pharmaceutical; and c. administering 500 μg to 1500 μg of vitamin B12 1 to 3 weeks prior to the first administration of the pharmaceutical, wherein the regimen is characterised by a reduction of toxicity and maintenance of antitumor activity of the pharmaceutical.”

(2) Judgment of February 2, 2017, IP High Court

It can be said that a skilled person would consider employing the cited invention to administer in combination with folic acid for administering MTA to a patient to reduce MTA toxicity and allow for dose-escalation while maintaining MTA's antitumor activity. However, it is not sufficient to admit that a skilled person could easily conceive of using vitamin B12 in combination to reduce MTA toxicity and maintain antitumor activity, based on the cited invention.

There is no teaching or suggestion in the cited documents that point out the problems associated with folic acid administered alone, nor is there any teaching or suggestion that would motivate the combination of something else, such as further reduction of MTA toxicity or maintenance of antitumor activity if combined with something other than folic acid.

The cited documents are different in use from the elements of the invention 1, in which folic acid and vitamin B12 are administered in combination to reduce the toxicity of antifolates and to maintain antitumor activity, and cannot be said to motivate or suggest the above elements.

3. **Zometa**

(1) Patent

Claim 1

“An agent for treatment containing 2-(imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid (Zoledronate) or pharmaceutically acceptable salts, wherein 4 mg of Zoledronate is to be administered intravenously over a period of 15 minutes to a patient in need of bisphosphonate treatment.”

(2) Judgment of December 24, 2014, IP High Court

The results of the clinical trials indicate no result that raises safety concerns during phase I and phase II, Therefore, even from the perspective of convenience for and reduction of burden on patients, it is difficult to find a motivation to further extend “five-minute” in the cited invention to “fifteen-minute” in the cited documents 1 and 2.

Therefore, it is difficult to find a motivation to further extend the administration time, that is, five-minute administration of 4 mg of zoledoronate, of which safety was confirmed in cited documents 1 and 2, to fifteen-minute.