Involvement of Anticancer Drugs in the Relief System for Adverse Drug Reactions in Japan

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**Objective:** The compensation scheme for adverse drug reactions in Japan was implemented more than three decades ago as relief system by regulatory agencies. Because of the high frequency of adverse drug reactions, anticancer drugs have been excluded from coverage by the relief system since its implementation. Requests have recently been made by some patient advocates for the expansion of relief coverage to include anticancer drugs. In response to these requests, the Ministry of Health, Labor and Welfare of Japan established a committee to discuss relief from anticancer drug-induced health damages in June 2011.

**Methods:** We conducted comprehensive research into the compensation scheme for adverse drug reactions in the world. We also investigated the situation of compensation and the committee for discussing inclusion of anticancer drugs into the relief system in Japan.

**Results:** Many countries including the United States and UK do not have relief or compensation schemes for no-fault compensation. We investigated whether a no-fault compensation system exists in Nordic countries (Sweden, Denmark, Norway and Finland), France, Germany, New Zealand and Taiwan in the world, although they offer different services from Japan. We also reviewed current situation and the fundamental difficulties associated with including anticancer drugs in the systems in Japan.

**Conclusions:** The present study investigated the current situation and the fundamental difficulties associated with including anticancer drugs in the systems in Japan and pointed out part of the reason why the committee could not conclude involvement of anticancer drugs in the relief system.

**Key words:** adverse drug reactions – relief system – compensation – anticancer drug – oncology

**INTRODUCTION**

Over the past decades, there have been significant adverse drug reactions (ADRs) caused by new and old drugs that gave rise to social problems around the world. Against occurrence of ADRs, there have been treated by health care insurance systems or lawsuits against pharmaceutical companies, etc. In addition to these systems, some countries have no-fault compensation schemes for ADRs. Japan also has this type of non-fault compensation system which is called relief system for ADRs in addition to the health insurance and lawsuits. A relief system for ADRs was established in Japan in 1979, triggered by the health damage caused by thalidomide, subacetemyelo-optico-neurpathy caused by clioquinol, etc. This system, with the purpose of promptly relieving patients...
who suffer from health damage resulting from ADRs, provides relief benefits for serious health damage in cases that may take a long time in the civil court. The resource for compensation is covered by levies placed on the pharmaceutical industry, and medical care expenses, medical allowances, disability pension etc. are provided as relief benefits (1−4).

Since its establishment, anticancer drugs have been excluded from coverage under the relief system for ADRs for the following reasons:

(i) Serious ADRs are very common with anticancer drugs.
(ii) Because of the life-threatening nature of cancer, use of anticancer drugs is inevitable for treatment of the disease.
(iii) Alternative treatments are extremely limited.

This particular situation for anticancer drugs applies not only to marketed products, but also to investigational products used in experimental studies such as clinical trials (5,6).

In recent years, requests have been made for the inclusion of anticancer drugs into the relief system coverage. Some patient advocates have been raising their voices in protest against the exclusion of anticancer drugs. Furthermore, relief expansion to anticancer drugs was called for in the statement, ‘Final proposal on validation of accidents for drug-induced hepatitis and restructuring of regulatory authorities’ submitted in April 2010 (7). The Ministry of Health, Labor and Welfare (MHLW) established a committee to discuss relief from anticancer drug-induced health damages in June 2011.

Under the above circumstances, discussions have been held on the possibility of providing relief benefits to patients who suffer from ADRs caused by anticancer drugs in Japan.

PATIENTS AND METHODS

We conducted comprehensive research into the relief system for ADRs in the world, the current status of ADRs associated with anticancer drugs in the world and the Committee on Anti-cancer Drugs in the Relief Systems for ADRs in Japan with reference to information published by various regulatory agencies, research reports from various study groups and regulatory agencies, and websites. To investigate situations in other countries, we conducted an exhaustive search of the literature in addition to research into the information published by overseas regulatory agencies.

RESULTS

ANALYSIS OF CURRENT SITUATION OF THE RELIEF SYSTEM FOR ADRs AND ADRs OF ANTICANCER DRUGS IN JAPAN

CURRENT SITUATION OF THE RELIEF SYSTEM FOR ADRs IN JAPAN

The relief system for ADRs in Japan is part of the relief services for adverse health effects, which is one of the missions of Pharmaceuticals and Medical Devices Agency (PMDA) (8). The relief is not provided as public social security benefit, instead using a strong characteristic of solatium based on the social responsibility of the pharmaceutical company in Japan. The scope of the Japanese relief system specifies patients who experienced serious ADRs resulting in hospitalization, disability or death. The relief systems cover both expected and unexpected ADRs of the drugs (including Stevens−Johnson syndrome), and it does not matter with ADRs described package insert or not. However, only ADRs caused by drug usage conducted in accordance with the package insert (i.e. indication, dosage and dose regimen) are covered by the system and ADRs caused by off-labeled use are not covered. The operating scheme of the relief services is illustrated in Fig. 1. Japanese relief services are provided to promptly relieve the patient who suffered from drug injuries and who claimed benefits to the PMDA. Once a claim is raised by patients, the PMDA requests a judgment from the Minister of Health, Labor and Welfare, and the Minister seeks consultation with the Pharmaceutical Affairs and Food Sanitation Council. The members of the Pharmaceutical Affairs and Food Sanitation Council review each claim by scientific point of view and make advises to Minister of MHLW whether to be compensated or not. Then, the patient receives a notice of evaluation and payment of benefits. If the claim is rejected by the PMDA, the patient has right to be treated by health care insurance systems or lawsuits against pharmaceutical companies. The finance of relief is funded by levies on the pharmaceutical companies (including pharmacies which produce drugs), which are divided into general and additional levies. Every pharmaceutical companies needs to pay general levies, and the rate of a levy is multiplied based on the total number of drug shipments by each company. Additional levies are contributions paid by the manufacturers whose pharmaceutical products are the direct cause of the ADRs. The rates of levies can be raised with increases in the number of claims, and the amount of levies has tended to increase recently. The levy rate has risen gradually, from 0.02/1000 at the establishment of the system in 1979 to 0.35/1000 in 2011. The sum total of levies in the 2011 fiscal year was 4337 million yen, and the sum total of benefits granted to patients was 2058 million yen (9). The benefits actually granted to patients are medical expenses, medical allowances (paid to reduce the burden of expenses other than medical expenses, as a monthly allowance of 35 000 yen), disability pension (taking into consideration the grade of disability and ranging from 180 000 to 220 000 yen/month), pension for raising handicapped children (taking into consideration the grade of disability and ranging from 55 000 to 70 000 yen/month), bereaved family pension (a monthly amount of ~200 000 yen for 10 years), lump-sum benefits for bereaved families (~7 million yen) and funeral expenses (~200 000 yen).

The number of claims from 2007 to 2011 totaled 4979, with an annual average of 996 claims. The number of approved cases for the same period was 4217, with an annual average of 843. The number of refused cases was 663, with an annual average of 133. The median processing time was an average of 6.4 months. Moreover, the latest data for the year 2011 show
that the number of claims was 1075, the number of approved
claims was 959 and the median processing time was
6.1 months (9). A total of 135 drugs were listed as excluded
from the relief system, including anticancer drugs and immu-
nosuppressants, as of April 2013 (10). Determination of
whether to exclude a drug from the relief system is made at
the time of the drugs approval based on the ADR data from
the preceding clinical studies by the Pharmaceutical Affairs
and Food Sanitation Council.

THE PRESENT SITUATION OF ADRS CAUSED BY ANTICANCER DRUGS IN JAPAN

The PMDA promptly receives and efficiently collects safety
information from pharmaceutical companies when cases of
serious ADRs caused by drugs and medical devices are
detected during the development and post-marketing periods.

Table 1 shows a summary of ADRs reported during the 6
years from 2005 to 2010 (the figure for the year 2010 repre-
sents data obtained up to December). The number of ADRs
caused by any drugs totals approximately 20 000–30 000
cases each year in Japan. No data are published on ADRs distin-
guishing between those caused by anticancer drugs and
those caused by other drugs, but data on fatal cases are
available by therapeutic category. We calculated anticancer
drug-caused fatal cases based on these data. A total of 200–
600 fatal cases that may possibly be related to drugs occurred
annually. Of these, fatal cases that may possibly be related to
anticancer drugs accounted for 259 (46.7%) in 2005, 219
(42.4%) in 2006, 180 (39.6%) in 2007, 216 (52.6%) in 2008,
217 (61.5%) in 2009 and 128 (49.6%) in 2010, revealing that
approximately half of the published deaths with a possible re-
lationship to drugs were potentially caused by anticancer
drugs (11).

FEATURES OF RELIEF SYSTEMS IN COUNTRIES OTHER THAN JAPAN

In many countries including the United States, the UK etc.,
although compensatory systems such as liability for damages
or the Product Liability Law exist, they do not have relief or
compensation systems for no-fault compensation. From our
comprehensive research, we found that a similar no-fault
compensation system for ADRs exists in various Nordic coun-
tries (Sweden, Denmark, Norway and Finland) (12–14),
France, Germany (15), New Zealand (16,17) and Taiwan (18)
in the world, although they seem to offer different services
from the system in Japan, as summarized in Table 2.
Table 2. An outline of no-fault compensation systems in each country

<table>
<thead>
<tr>
<th>Scope of relief coverage</th>
<th>Sweden</th>
<th>Finland</th>
<th>Norway</th>
<th>Denmark</th>
<th>New Zealand</th>
<th>Germany</th>
<th>Taiwan</th>
<th>France</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exception drugs</td>
<td>External medicines, naturopathic drugs, homeopathic drugs</td>
<td>Herbal products, homeopathic drugs</td>
<td>None</td>
<td>Naturopathic drugs, homeopathic drugs, vitamins/mineral supplements</td>
<td>None</td>
<td>None</td>
<td>Herbal products, traditional Chinese medicines</td>
<td>None</td>
<td>Anticancer drugs</td>
</tr>
<tr>
<td>Class or severity of covered ADRs</td>
<td>Unexpected ADRs</td>
<td>Unexpected adverse reactions</td>
<td>Does not apply when accepting the type and/or severity of damage by the patient is rational</td>
<td>Does not apply when accepting the type and/or severity of damage by the patient is rational. Does not apply when the amount of compensation is ≤ 3000 DKK</td>
<td>Does not apply to those inevitably or generally occurring as a result of treatment</td>
<td>Death or marked injuries to the body or health. ADRs exceeding acceptable limits</td>
<td>Serious, death. Temporary disability (≥ 6 months), persistent disability of a certain degree or more severe, ADRs leading to significant difficulties such as definitive inability to carry out occupational activities etc. Does not apply to those judged as normal based on the initial health status</td>
<td>Serious, death. Also applies to known events listed in package inserts</td>
<td></td>
</tr>
<tr>
<td>Contents of relief</td>
<td>Calculated based on the civil liability law (with upper limits)</td>
<td>Calculated based on the act on compensation</td>
<td>Calculated based on the act on liability for damage (with upper limits)</td>
<td>Calculated based on the act on liability for damage (with upper limits)</td>
<td>Medical care (in-kind benefits), income compensation (with upper limits), disability/survivor lump-sum payments etc</td>
<td>Compensation for damage (with upper limits)</td>
<td>Compensation for damage (with upper limits)</td>
<td>Uniform payment</td>
<td></td>
</tr>
<tr>
<td>Judgment of proper usage of drugs</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rights to demand other compensation</td>
<td>Extinguished upon receipt of compensation</td>
<td>No limits</td>
<td>Cannot demand compensation from pharmaceutical companies</td>
<td>Extinguished upon receipt of compensation</td>
<td>None</td>
<td>No limits</td>
<td>No limits</td>
<td>Extinguished upon receipt of compensation</td>
<td>No limits</td>
</tr>
<tr>
<td>Source of relief fund</td>
<td>Insurance fees from voluntary subscribers</td>
<td>Insurance fees from voluntary subscribers</td>
<td>Insurance fees from mandatory subscribers</td>
<td>Tax</td>
<td>Taxes and fees on income earners</td>
<td>Insurance fees from pharmaceutical companies</td>
<td>Levies on pharmaceutical companies</td>
<td>Subsidies from governmental health insurance and insurance companies</td>
<td>Levies on pharmaceutical companies</td>
</tr>
</tbody>
</table>
scope of relief coverage in the Nordic countries, Germany and Taiwan is focused on drug-induced injuries. However, in the system used in France, compensation for drug-induced injuries is a part of the compensation system for all medical accidents. The system of New Zealand is similar to that in France, with the scope of coverage being injuries from accidents. In the Nordic countries and France, the amount is individually calculated for every case as a substitute for a civil action. For example, under the system of the Nordic countries, the amount of compensation depends on age, situation of employment etc., and the scope of coverage extends only to ADRs that cannot be predicted. Even if the system in Japan provides payments, lawsuits can still be instituted, and payment is defined uniformly in the system rather than being decided individually. ADRs described in package inserts are also still covered by the relief system in Japan. Furthermore, the ratio of acceptance in Japan is higher than that in any of the other countries investigated.

In foreign countries, ADRs caused by anticancer drugs are not necessarily placed outside the scope of relief or compensation. However, in many countries, judgment systems have been put in place for considering the stage of disease, stage of cancer, grade of ADR, possible expectations for ADRs etc. As a result of judgment, however, victims are rarely compensated for ADRs caused by anticancer drugs, and few track records of compensation for ADRs of anticancer drugs are available at present (Table 2).

**Discussions in the Committee on Anticancer Drugs in the Relief Systems for ADRs in Japan**

In response to requests for expansion to cover anticancer drugs under the relief systems in Japan, the ‘Committee on Anticancer Drugs in the Relief Systems for ADRs in Japan’ was established in June 2011 by the MHLW. This committee comprises experts in the fields of medicine, pharmacy, law, economics and statistics, along with the members representing patients and the media, and 11 meetings have been held to date (19). Discussions have taken place after obtaining a wide range of opinions from related parties. A summary of the opinions provided in the meetings is presented in Table 3.

The opinions from each related party can be divided into two groups.

The academic societies and pharmaceutical manufacturers’ association were reluctant to include anticancer drugs in the relief system for ADRs. One of the patient advocate groups, YAKU-HI-REN, strongly supported to include anticancer drugs in the relief system, while the other two advocates did not clarify their positions on this matter.

(i) The academic societies and pharmaceutical manufacturers’ association also expressed their views that exclusion of anticancer drugs from the current system is reasonable. With regard to the exclusion, one patient advocate (YAKU-HI-REN) insisted that differentiating anticancer drugs from other drugs is wrong recognition.
Table 3. Summary of the opinions provided in the Committee on Anticancer Drugs in the Relief Systems for ADRs in Japan

<table>
<thead>
<tr>
<th>Questions</th>
<th>Physicians and academic societies</th>
<th>Patient advocates</th>
<th>Manufactures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Including anticancer drugs in the relief system for ADRs</td>
<td>JSCO</td>
<td>YAKU-HI-REN</td>
<td>FPMAJ</td>
</tr>
<tr>
<td>What is your opinion regarding inclusion of anticancer drugs in the relief system for ADRs?</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Is there a difference between anticancer drugs and other drugs in the relief system?</td>
<td>Yes, serious ADRs are inevitable for anticancer drugs</td>
<td>No, Anticancer drugs are the same as other drugs</td>
<td>Yes, serious ADRs are inevitable for anticancer drugs</td>
</tr>
<tr>
<td>What is your opinion on the exclusion of anticancer drugs from the current system?</td>
<td>Agree</td>
<td>Disagree. All drugs should be included</td>
<td>Agree</td>
</tr>
<tr>
<td>What is your opinion on the scope of coverage?</td>
<td>Determining ways to limit the scope is difficult; it also depends on prognoses</td>
<td>Limitation of the scope is difficult</td>
<td>–</td>
</tr>
<tr>
<td>2. Impacts on the actions of the people involved</td>
<td>Hesitate to administer anticancer drugs</td>
<td>Medical care will not be diminished</td>
<td>Concerned about diminishing medical care</td>
</tr>
<tr>
<td>Impact on health care professionals?</td>
<td>Hesitate to administer anticancer drugs</td>
<td>Specialists become reluctant to use anticancer drugs, and doctors in general practice use them more frequently</td>
<td>Concerned about diminishing medical care</td>
</tr>
<tr>
<td>Impact on patients?</td>
<td>Will not be able to receive world-standard treatment</td>
<td>Relief will be given promptly without trial for damages due to ADRs</td>
<td>–</td>
</tr>
<tr>
<td>Impact on pharmaceutical companies?</td>
<td>Hesitate to develop anticancer drugs</td>
<td>Concerned about more drug lags</td>
<td>Concerned about more drug lags</td>
</tr>
<tr>
<td>Impact on litigation action?</td>
<td>Lawsuits against physicians increase</td>
<td>Lawsuits decrease</td>
<td>Lawsuits increase overseas</td>
</tr>
<tr>
<td>3. Benefits and burdens</td>
<td>Society as a whole should bear cost</td>
<td>Inquiries on the relief system increase dramatically</td>
<td>Levies should be included in drug price</td>
</tr>
<tr>
<td>What is your opinion regarding who shall bear costs and in what proportion?</td>
<td>Involve enormous cost</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>What is your opinion on operating costs?</td>
<td>Increase</td>
<td>Result in increased drug price</td>
<td>Should be passed on to drug development</td>
</tr>
</tbody>
</table>

Anti-cancer drugs in relief system in Japan
The other two patient advocates raised concern that the inclusion of anticancer drugs might diminish the range of medical care and worsen the drug lag.

(ii) A majority pointed out that active development of new methods for the treatment of cancer, provision of ADR information to patients and establishment of a consulting system for cancer patients are more important than inclusion of anticancer drugs in the relief system for ADRs.

For over 1 year, the Committee on Anticancer Drugs in the Relief Systems in Japan had 11 meetings to discuss whether to include ADRs caused by anticancer drugs in the relief system or not. In the first several meetings, different views divided into two groups described above become apparent. In spite of efforts to fill the gap in the two groups, there seemed to be no room for compromise in the two groups in the meeting. Therefore, the committee had to abandon the discussion.

Finally, the Committee on Anticancer Drugs in the Relief System for ADRs in Japan decided not to recommend including anticancer drugs in the Japanese relief system, and discussion regarding this issue ended in August 2012.

DISCUSSION

None of the papers have previously discussed the issues involved in whether to include ADRs caused by anticancer drugs within the Japanese relief system for ADRs or not.

The Japanese relief system for ADRs is intended to address adverse health effects causally related to drugs, requiring hospitalization or a higher degree of medical intervention, and caused by usage complying with the package insert for the drug. There are some exceptional cases in the relief system. In the drugs with a poor safety profile, patients cannot receive compensation, if the patients understand the risk of occurrence of ADR in advance and desire treatment with the drugs. From this perspective, anticancer drugs have been excluded from the Japanese relief system for ADRs.

If we include ADRs caused by anticancer drugs in the Japanese relief system for ADRs, consideration should be given to the scope of coverage, judgment criteria for the causality of the relationship and proper usage, and disadvantages of including ADRs due to anticancer drugs in the relief system. To define the scope of coverage of the system, the degree of cancer progression (stages, pre/post-surgery, primary/recurrence, early/advanced/terminal stage) of the patient needs to be taken into consideration. The idea of including some anticancer drugs in the system seems reasonable. In clinical trials, drugs subject to compensation are actually determined by each pharmaceutical company based on the Japan Pharmaceutical Industry Legal Affairs Association guidelines. Currently, anticancer drugs with a small number of adverse events may be subject to compensation depending on the pharmaceutical company (20). Regarding the judgment criteria for causality of the relationship and proper usage, ensuring a reliable judgment system would not be easy, given
the difficulties in judging the causal relationship between anticancer drugs and adverse health effects, and shortages of cancer medication experts despite the need for a large number of such experts to judge causality. Furthermore, anticancer drugs are often not administered in accordance with the proper indications, dosage and administration and precautions described in the package insert, or with standard therapies specified in the guidelines of academic societies. Applying the judgment criteria for proper usage of anticancer drugs in a uniform manner under such circumstances would be problematic. In addition, the number of fatal cases related to anticancer drugs accounts for about half of the fatal cases related to all drugs as shown in Table 1, cost would be a major concern if we include ADRs caused by anticancer drugs in the relief system. Levies from pharmaceutical companies have kept increasing since the establishment of the relief system (9). It would become a big issue who pays increased cost.

The Committee on Anticancer Drugs in the Relief System for ADRs in Japan anticipated following actions if we include ADRs caused by anticancer drugs in the relief system. Exercising the relief system with the addition of ADRs induced by anticancer drugs raises concern that physicians may hesitate to use anticancer drugs, and patients may thus end up with fewer treatment options. Furthermore, application of the system may result in pharmaceutical companies becoming reluctant to develop or market anticancer drugs in Japan due to concerns regarding the risk of lawsuits and costs associated with increasing numbers of claims on the relief system. Establishment of the system may also result in the inclusion of ADRs due to anticancer drugs alone as items subject to payment of relief benefits, leading to unfairness between adverse health effects due to anticancer drugs and those due to radiotherapy, surgery etc. This issue thus also extends beyond anticancer drugs, to involving surgery and radiotherapy.

Comparing the relief system of Japan with that of other countries, ADRs caused by anticancer drugs are not necessarily placed outside the scope of relief or compensation in foreign countries. However, judgment systems have been put in place for considering the stage of disease, stage of cancer, grade of ADR, possible expectations for ADRs etc. in other countries. As a result of judgment, victims are rarely compensated for ADRs caused by anticancer drugs, and few track records of compensation for ADRs caused by anticancer drugs are available at present. The ratio of acceptance in Japan is highest among the countries that have no-fault compensation. Considering the high acceptance rate in the past, it may be difficult to lower acceptance rates of anticancer drugs like other countries.

Starting June 2011, the Committee on Anticancer Drugs in Relief Systems for ADRs in Japan discussed whether to include ADRs due to anticancer drugs in the relief system for ADRs. In August 2012, the committee concluded to put an end to discussion without any concrete proposals. During the discussion, a substantial difference in opinions was noted between a patient advocate group (YAKU-HI-REN) and other patient advocate organizations. The former group considers that anticancer drugs should also be included in the relief system for ADRs and the relief system should form a substitute for compensation resulting from liability for damage. Conversely, the latter group worries that including anticancer drugs may have unintended consequences which may adversely impact the welfare of both patients and healthcare providers. We understood that the committee could not reach a consensus on whether or not to include ADRs of anticancer drugs in the relief system for ADRs because of the wide gap between these two positions. If the committee were going to fill a gap based on the difference in value, scientific discussion by the expert in the fields of medicine, pharmacy, law and statistics like this time might not be right. Therefore the authors also believe that the relief system for ADRs in Japan does not need to include anticancer drugs in these situations.

Given the complicating circumstances as mentioned above and the excellence of the Japanese relief system for ADRs even from an international standard, we consider that ADRs due to anticancer drugs should not be immediately included in the current relief system for ADRs.

CONCLUSIONS

Japan is one of the few countries in the world with a long running and excellent relief system for ADRs. At present, the relief system for ADRs in Japan excludes anticancer drugs and has not included ADRs caused by anticancer drugs so far. We consider that ADRs due to anticancer drugs should not be immediately included in the current relief system for ADRs.

Conflict of interest statement

Hideki Maeda is an employee of Astellas Pharma Inc.

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