Current Topics

Challenges of Drug Delivery Systems That Contribute to Cancer Chemotherapy

Application of Hospital Preparations for Cancer Treatment, and an Approach toward Their Commercialization

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In Japan, pharmacists who are in consultation with doctors independently prepare medications in an attempt to meet the needs of patients in the hospital. In particular, the need for hospital preparations to treat cancer is high and diverse. However, unlike government-approved medications, independently and individually prepared hospital preparations raise concerns about their effectiveness, safety, economic efficiency, quality control, etc. One way to address these concerns is to commercialize these preparations and to understand the difference between necessity and demand from various points of view. We have conducted nation-wide utilization surveys and evaluated the literature on hospital preparations. On the basis of the findings of this survey, we have concluded that pharmaceutical companies and the government need to implement the commercialization of hospital preparations in clinical practice. In this report, we discuss the significance of commercialization of hospital preparations, concerns regarding pharmaceutical preparations, and our recent efforts on cancer treatment. We hope to continuously contribute to society and to medical care by improving individualized care and by commercializing medications needed in clinical practice.

Key words hospital preparation; commercialization; cancer treatment

1. INTRODUCTION

In recent years, the development of medications with novel mechanisms of action and generation of new formulations from existing medications have benefited many patients. According to the Ministry of Health, Labour and Welfare of Japan, about 30000 medications can be prescribed or purchased at hospitals and pharmacies across Japan. However, in reality, meeting the diverse and unique needs of patients is difficult by treating them only with existing approved medications, which might delay the recovery. Therefore, hospital pharmacists who work in consultation with doctors often independently prepare pharmaceutical medications, *i.e.*, hospital preparations, to meet such needs. Only those hospital pharmacists who have studied pharmaceutical sciences at hospitals are authorized to prepare hospital preparations, and the importance of this policy has been established in Japan.

However, compared to government-approved medications, hospital preparations are associated with concerns regarding effectiveness, safety, economic efficiency, and quality control. These concerns can be addressed by encouraging the marketing and commercialization of hospital preparations that are prepared nation-wide and are high in demand. Thus far, from the Fourth Sciences Subcommittee of the Japanese Society of Hospital Pharmacists, we have collected feedback given by many hospital pharmacists, and conducted nation-wide utilization surveys and evaluated the literature on hospital preparations. On the basis of these findings, we reorganized the in-

formation on hospital preparations for their commercialization and requested pharmaceutical companies and the government to act on this information.

In this report, we discuss the significance of the commercialization of hospital preparations, concerns regarding these pharmaceutical preparations, and our recent efforts on cancer treatment.

2. PURPOSE OF COMMERCIALIZATION OF HOSPITAL PREPARATIONS

Because hospital preparations are not regulated according to the Pharmaceutical Affairs Law, there are serious concerns over their use. First, since hospital preparations must be administered within the hospital, their use is limited. In other words, patients of one hospital have no access to hospital preparations provided by another hospital, creating gaps and inconsistency in treatment for patients. Commercialization of hospital preparations would facilitate their consistency and availability across hospitals in Japan, benefitting many patients.

Although the Japanese Society of Hospital Pharmacists has issued guidelines for quality control of hospital preparations, not all hospitals adhere to them. If hospital preparations are produced and distributed by pharmaceutical companies, their production, distribution, and administration would comply with good manufacturing practice (GMP), good vigilance practice (GVP), and good post-marketing study practice (GPSP) guidelines, which would facilitate their proper use in clinical practice. Furthermore, despite the fact that hospital

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preparations are approved by the ethics review board of each hospital, sufficient indemnification is not provided in the case of critical health damage. When hospital preparations would need to be approved *via* the Pharmaceutical Affairs Law, safety measures would be implemented by pharmaceutical companies per the instructions of regulatory authorities. Relief systems for patients developing adverse drug reactions would then become applicable, and patients would become eligible for indemnification in the case of health damage.

The benefits of commercialization of hospital preparations extend beyond hospitals and patients. The success rate of new drug development is known to be 1 in 30000, and between 9 and 17 years of research and development is typically required before a new drug is introduced into the market. Thus, new drug development presents a significant risk to pharmaceutical companies. However, since hospital preparations are already in use and have been evaluated in clinical practice, the risks associated with their use is effectively minimized. In particular, hospitals would support and actively cooperate during the developmental stages of commercialization of hospital preparations that are in high demand, providing clear reasons to the regulatory authorities about the necessity of hospital preparations, which could help at the time of the submission of an application, and perhaps also expedite approval.

3. HOSPITAL PREPARATIONS REQUIRING COMMERCIALIZATION

For the commercialization of hospital preparations, verification of their stability and safety is essential, and evaluation of the evidence related to the safety and effectiveness of these medications is important. Additionally, the necessity of commercialization needs to be assessed through nation-wide utilization surveys and by consideration of the economic impact on the pharmaceutical industry. The following factors regarding hospital preparations requiring commercialization need to be carefully investigated: (1) whether concrete evidence exists, (2) whether a proper dosage and administration method can be determined, (3) whether the safety level is high, (4) whether the preparation is profitable, and (5) whether the quality can be maintained during transport. Hospital preparations that meet these requirements and are considered important by hospital pharmacists for market use should be actively promoted for commercialization.¹⁾ The characteristics of such desired hospital preparations are listed in Table 1. However, commercialization of most of the hospital preparations is difficult, for varying reasons (Table 2). Nonetheless, these difficult-to-commercialize medications (those which need to be modified by hospitals in response to the unique conditions of patients) provide opportunities for pharmacists to completely exercise

Table 1. Reasons Why Commercialization of Hospital Preparations Is Necessary

High frequency of usage
Used in large quantities
Used at many facilities
Requires extensive formulation techniques
Requires most up-to-date facilities and expensive precision measuring instruments
Potential hazards to pharmacists in charge of preparation

their professional skills.

4. EXAMPLES OF APPROACHES FOR THE COMMERCIALIZATION OF HOSPITAL PREPARATIONS

In our recent approaches, we assessed the following hospital preparations used in medical care for cancers.

4.1. Dye Preparations for Sentinel Lymph Node Biopsy

The basic treatment for early-stage breast cancer is surgery, and metastasis to lymph nodes is one of the factors that affect the prognosis of this cancer. Currently, determination of whether the removal of axillary lymph nodes is necessary requires that a biopsy of the sentinel lymph nodes identified by dye or radioisotopes (RIs) be performed because this is the region where cancer cells from a tumor first metastasize. However, in Japan, dye preparations needed for sentinel lymph node biopsy (SLNB) have not been commercialized; hence, these dyes have been replaced by hospital preparations or by the unapproved use of existing drugs. Therefore, we investigated the literature on this biopsy method and evaluated the effectiveness and safety, costs related to formulation techniques and production, and overseas commercial market conditions of the dye preparations. Our findings suggested that SLNB is being established as a standard diagnostic procedure for early-stage breast cancer overseas,²⁾ and that dye preparations for SLNB are already commercially available; these findings clarified the need for commercialization of such dye preparations in Japan.³⁾

Furthermore, we conducted surveys on the preparations used for SLNB at 300 Japanese hospitals and found that SLNB was performed using dye preparations that were not up to the mark in 80% of the hospitals (Fig. 1). The survey also suggested that almost 75% of the pharmacists requested the commercialization of these dye preparations. Eventually, with the support of the Japanese Breast Cancer Society, indigo carmine and indocyanine green, available since September 2009 for SLNB, were added to the list of dye preparations indicated for the “identification of sentinel lymph nodes in breast cancer and malignant melanoma.”

4.2. Topical Metronidazole for Treatment of Cancerous Malodor

Cancerous malodor is an intense smell emitted from cancerous skin ulcers of patients with advanced cancer, and is thought to be caused mainly by rotten and dead focal tissues infected with anaerobic bacteria such as *Bacteroides* spp. and *Peptostreptococcus* spp.⁴⁾ Almost 4% of all breast cancer patients have been reported to develop cancerous skin

Table 2. Factors Affecting the Commercialization of Hospital Preparations

Rate of effectiveness is procedure-dependent and effectiveness is difficult to determine
Evaluation of drug efficacy has not been specified
Composition is not uniform
Potential drug interactions
Existing commercialized drugs are sufficient
High drug toxicity and concerns regarding safety
Unlikely to be profitable to recover necessary costs
Extremely large in size
Extremely difficult to develop protocols for clinical trials
Unable to have support from related societies and professional organizations

Fig. 1. Concerns in the Process of Dye Preparation for SLNB

Fig. 2. Effectiveness of Topical MTZ

Fig. 3. Medications in Need of Commercialization to Treat Malodor in Cancer Patients

ulcers with malodor. This malodor remarkably decreases the quality of life (QOL) of patients by causing serious mental stress, and it raises concerns for the family and healthcare providers involved. However, since no approved medications for cancerous malodor are available in the Japanese market, hospitals use topical metronidazole (MTZ), which is effective for the treatment of anaerobic bacteria, to formulate hospital preparations.

Therefore, we evaluated information regarding MTZ and found that topical MTZ is commercially available. The effectiveness of MTZ has already been established on the basis of the results of placebo-controlled randomized studies, and the medication has been endorsed in the guidelines of the World Health Organization and the American Society of Clinical Oncology.^{5,6)} Therefore, we conducted surveys on the preparation and utilization of topical MTZ at 500 hospitals in Japan to evaluate its necessity, and confirmed the effectiveness of this medication (Fig. 2). Furthermore, 80% of the participating hospitals requested commercialization of medications for malodorous cancerous skin ulcers and particularly demanded the commercialization of topical MTZ⁷⁾ (Fig. 3). As of December 2012, this hospital preparation is under discussion by the investigative commission of the Ministry of Health, Labour and Welfare of Japan, and clinical trials aimed at commercialization and sponsored by pharmaceutical companies are in progress.

4.3. Necessity of Availability of Anticancer Agents in Multi-Dose Vials Anticancer agents tend to be costly, and their dosage is strictly adjusted according to a patient's body surface area and weight, since any excess medication needs to be discarded in Japan. In contrast, in other countries such as the U.S., anticancer agents are commercially available in multi-dose vials so that multiple patients can be treated using 1 vial, which eliminates medication wastage. Hence, we evaluated the necessity of introducing drugs in multi-dose vials in Japan. First, for obtaining basic information on the need for multi-dose vials in Japanese hospitals, we conducted field surveys to study the total cost and discarded amounts of anticancer agents across 6 hospitals in Japan. Four medications are available in multi-dose vials in the U.S.: cisplatin, carboplatin, paclitaxel, and docetaxel. We included bortezomib in our survey for reference, because it is costly and excess is often discarded in hospitals. We investigated the discarded amount and calculated the cost of the medications discarded per the price range in Japan. The results suggested that the total cost of the discarded amounts of the 4 medications was approximately 40 million yen annually, and increased to 150 million yen annually when the cost of disposed bortezomib was included (Table 3). Future investigations across many other hospitals might reveal significant economic losses due to the wastage of unused medications. In order to compensate

Table 3. Disposed Amounts of Anticancer Agents and the Associated Cost

Drugs	Total number of cases	Total preparation amount	Total discarded amount	Total loss from discarded medications	Rate of discard (total amount discarded/total preparation)	Largest amount discarded	Largest cost associated with the loss
	Case	mg	mg	Yen	%	mg	Yen
CDDP	370	21150	678	124896	3.2	12.0	2322
CBDCA	344	135550	5996	505378	4.4	120.0	12225
PTX	458	65560	5067	1343213	7.7	39.0	11975
DOC	253	20500	1372	1348450	6.7	19.0	18677
BOR	148	444	175	9637643	39.5	2.0	109956

CDDP: cisplatin; CBDCA: carboplatin; PTX: paclitaxel; DOC: docetaxel; BOR: bortezomib. Total loss incurred from the discarding of the 4 medications (excluding BOR): $3321937 \text{ yen} \times 12 \text{ (1 year)} = 39863232 \text{ yen}$. Total loss from the discarded of all the 5 medications: $12959580 \text{ yen} \times 12 \text{ (1 year)} = 155514963 \text{ yen}$.

for this loss, the use of multi-dose vials in Japan is necessary. We have begun reviewing this objective in 2012, and hope to address this issue from multiple viewpoints.

5. CONCLUSION

Hospital preparations are an achievement of practical pharmaceutical science that involves the integrated disciplines of formulation chemistry and technique, pharmacology, clinical medicine, and pharmacokinetics. In clinical practice, if hospital pharmacists are able to independently prepare medications that are appropriate for the conditions of each patient, patients may benefit greatly, and the expertise and skills of hospital pharmacists will improve. However, there are concerns regarding the quality of such preparations and the environment in which these medications are prepared in Japanese hospitals. Although commercialization of hospital preparations is necessary, many issues and challenges need to be considered. In particular, the need for hospital preparations to treat cancer are high and diverse. By improving individualized care, and by commercializing medications that are in high demand in clinical practice, we hope to continuously contribute to society and medical care.

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