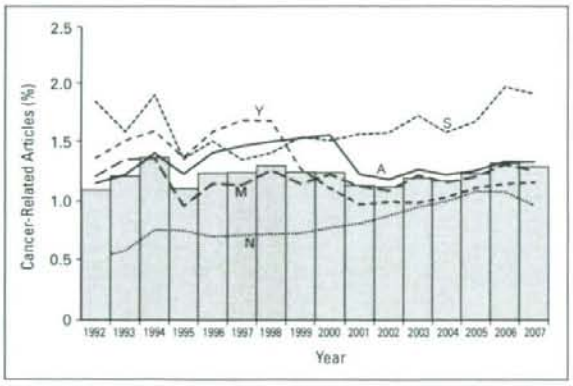

Fig 2. Ratio of cancer-related articles to total number of articles. Bar indicates five newspapers taken together (circulation = 27,310,000). A, *Asahi* (circulation = 8,090,000); M, *Mainichi* (circulation = 3,970,000); Y, *Yomiuri* (circulation = 10,020,000); S, *Sankei* (circulation = 2,190,000); N, *Nihon Keizai* (circulation = 3,040,000).

the following order: therapy (n = 4,813, 29.8% of total cancer-related articles), obituary (n = 3,401, 21.1%), surgery (n = 2,386, 14.8%), Ministry of Health, Labour and Welfare (n = 1,145, 7.1%), litigation (n = 1,048, 6.5%), development (n = 861, 5.3%), chemotherapy (n = 826, 5.1%), and preventive examination (n = 741, 4.6%).

The peak years for the ratio of articles containing each keyword to the total number of articles are shown in Figure 5. The figure shows three peaks: the first in 1992 to 1997 (n = 8), the second in 1998 to 2003 (n = 6), and the third in 2004 to 2007 (n = 18).

The present study shows that cancer is a topic of major interest in newspapers. Approximately 1.0% to 1.5% of the total number of articles (or 30 to 45 articles per day) in the five major newspapers were related to cancer. Even when we deduct the number of obituary articles, which accounted for 21% of the total cancer articles, we see that newspapers presented cancer information to many citizens.

The proportion of cancer articles to total articles remained stable from 1992 to 2007. These findings are contrary to the perception of medical professionals that public interest in cancer has increased with its morbidity because of the increase in the aging population.[3] Interestingly, *Nihon Keizai* newspaper, which specializes in the economy, commerce, and business, published an increasing number of cancer articles. Cancer is of interest to the economic world as well as the world of medicine, and this situation in Japan is comparable to that in other developed countries.[4]

Analysis by each cancer lesion showed that the total number of cancer articles was higher with regard to cancers with higher morbidity and mortality, such as lung, breast, stomach, and colon and rectal (Fig 3A). The number of articles per 1,000 cancer patients was higher in the following types of cancer: brain and CNS; hematologic; breast; and lower stomach, colon, and rectal. Although obituaries occurred at almost the same frequency with any type of cancer, specific cancers, such as those of the brain and CNS and hematologic malignancies (Fig 3B), were presented to the general public with greater frequency. It is noteworthy that the number of articles on hematologic malignancies was relatively large. This is likely because there were a high number of articles on diagnosis and therapy. Cancer articles in newspapers are influenced by the development of new cancer therapy. For example, chemotherapy or new drugs (rituximab [Rituxan; Genentech Inc, South San Francisco, CA; Biogen Idec, Cambridge, MA], imatinib mesylate [Gleevec; Novartis Pharmaceuticals Corp, East Hanover, NJ], and so on) are featured in articles on hematologic malignancies,[5] and therapeutic radiology, chemotherapy, and

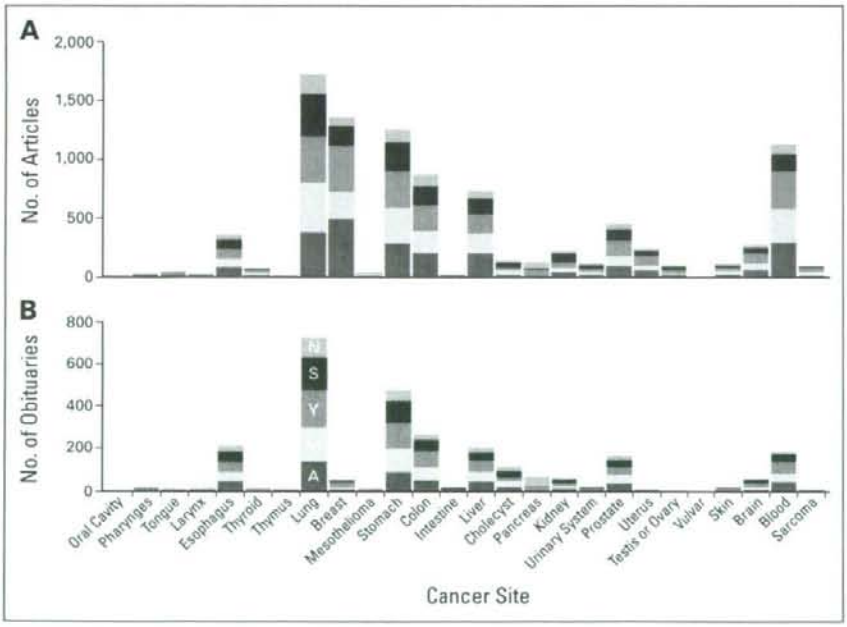

Fig 3. (A) Number of articles classified by cancer lesion in 2007. (B) Number of obituary-related articles according to cancer sites in 2007. A, *Asahi* (circulation = 8,090,000); M, *Mainichi* (circulation = 3,970,000); Y, *Yomiuri* (circulation = 10,020,000); S, *Sankei* (circulation = 2,190,000); N, *Nihon Keizai* (circulation = 3,040,000).

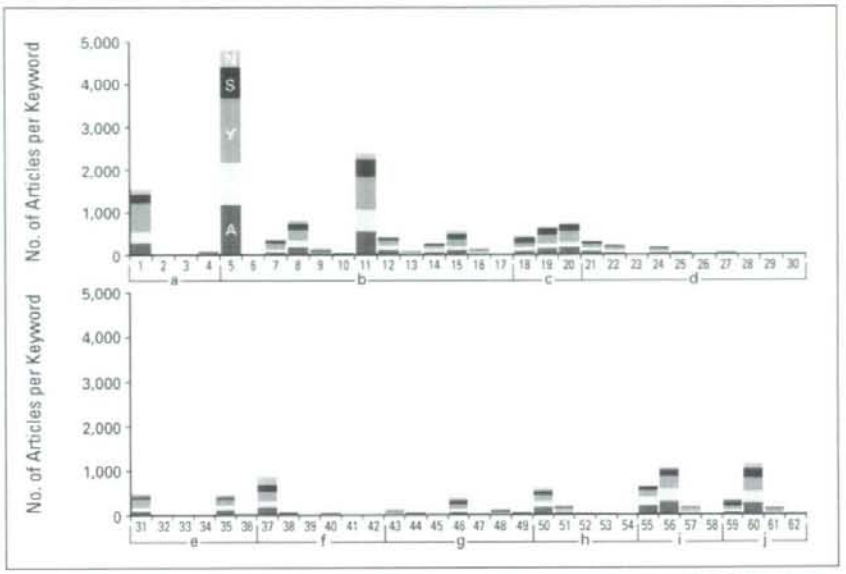

Fig 4. Numbers of articles for each keyword in 2007. Bar indicates five newspapers taken together (circulation = 27,310,000). (a) Diagnosis-related words: 1, diagnosis; 2, radiologic diagnosis; 3, pathologic diagnosis; 4, positron emission tomography; (b) therapy-related words: 5, therapy; 6, medical oncology; 7, radiation therapy; 8, chemotherapy; 9, new drug; 10, immunotherapy; 11, surgery or operation; 12, palliative care; 13, home care; 14, end of life or hospice; 15, side effect; 16, complication; 17, adverse effect; (c) prevention-related words: 18, cigarette, tobacco, or smoking; 19, prevention; 20, preventive examination; (d) policy-related words: 21, policy; 22, disparity; 23, uniformity or equalization; 24, Basic Act on Cancer Management; 25, cancer registration; 26, doctor fee not covered by insurance (out of pocket money); 27, advisor or counselor; 28, cancer information center; 29, cancer hospital; 30, cancer refugee (new word to represent a patient who cannot receive standard cancer therapy); (e) words related to medical societies: 31, medical society; 32, Japanese Cancer Association; 33, Japanese Society of Medical Oncology; 34, Japan Society of Clinical Oncology; 35, board certified physician; 36, oncologist; (f) words related to drug development: 37, development; 38, clinical trial; 39, physician-directed clinical trial; 40, Pharmaceutical Affairs Law; 41, Pharmaceuticals and Medical Devices Agency; 42, new drug and drug approval; (g) research-related words: 43, clinical research; 44, basic science research; 45, molecular science research; 46, genetics; 47, immunology; 48, epidemiology; 49, tissue engineering; (h) patient-related words: 50, patient's wish; 51, patient advocacy group; 52, self-import medication or unapproved drug; 53, reproduction; 54, advocacy; (i) litigation-related words: 55, litigation or lawsuit; 56, court case; 57, medical accident or medical error; 58, medical conflict; (j) other words related to cancer: 59, National Cancer Center; 60, Ministry of Health, Labour and Welfare; 61, Ministry of Education, Culture, Sports, Science and Technology; 62, Ministry of Finance. A, *Asahi* (circulation = 8,090,000); M, *Mainichi* (circulation = 3,970,000); Y, *Yomiuri* (circulation = 10,020,000); S, *Sankei* (circulation = 2,190,000); N, *Nihon Keizai* (circulation = 3,040,000).

surgeries are often seen in brain and CNS malignancies. Our study did not reveal that Japanese newspapers focused on reports of celebrities with cancer, whereas the mass media in Western countries promotes interest in a particular disease, for instance, Parkinson's disease, HIV/AIDS, or spinal injury when a celebrity suffers from it.[6-8]

As for keyword analysis, commonly seen keywords were therapy (29.8%), obituary (21.1%), and diagnosis (9.6%). This is probably because such articles attract readers' attention more frequently compared with articles involving areas in which medical professionals are interested, such as prevention, palliative care, medical system, and pharmaceutical administration. Articles on these areas are posted in professional journals and discussed at society meetings but do not often appear in newspapers. Our analysis suggests that there are limitations in distributing cancer-related information to the general public via newspapers. Rather, the Internet or free papers might be more effective in providing cancer-related information, as these media target particular readers' interests.[9,10] It should be noted that the phrase "the Ministry of Health, Labour and Welfare" occurred in 7.1% of the cancer articles. In Japan, major newspapers obtain most of their information from the press club of the Ministry of Health, Labour and Welfare. The dependency on the ministry may influence the distribution of cancer articles.

As for trends in the appearance of each keyword, "development," "prevention," "cigarette," and "National Cancer Center" occurred frequently during the period between 1992 and 1997. This can be explained by the following facts on the era: a new policy named the Second Term Comprehensive 10-Year Strategy for Cancer Control was implemented in 1994[11]; lung cancer came to be identified as the primary type of cancer causing deaths in Japan; and tobacco companies were penalized in relation to passive smoking. From 1998 to 2003, the keywords "gene," "new medicine," "clinical trial," "the Ministry of Health, Labour and Welfare," and "the Ministry of Education, Culture, Sports, Science and Technology" appeared frequently. The Millennium Project of 2000, which was directed by the government to confront the rapidly aging society, likely contributed to the appearance of these words. The phrase "medical incident" also occurred in this period. Multiple medical accidents, such as one involving a 16-year-old patient receiving chemotherapy who became a victim of iatrogenic overdose, were reported to the public at this time. More keywords reached a peak in the period between 2004 and 2007 than in the period between 1992 and 1997 or 1998 and 2003. Most keywords were related to cancer therapy (eg, therapy, surgery or operation, diagnosis, chemotherapy, preventive examination, palliative care, radiation therapy, positron emission tomography, and home care). The

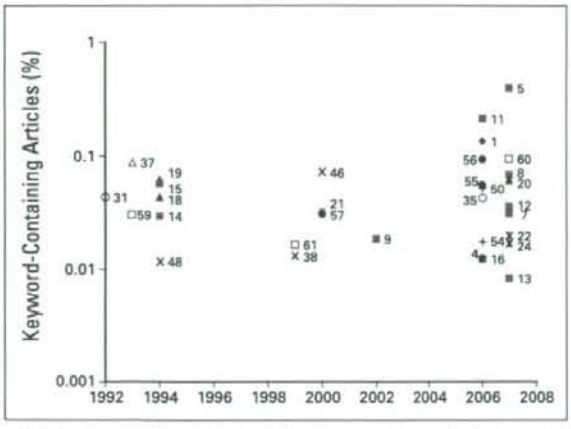

Fig 5. Peak years of the ratio of each keyword appearing in articles to the total number of articles. ◆ Diagnosis-related words; ■ therapy-related words; ▲ prevention-related words; * policy-related words; ○ words related to medical societies; △ words related to drug development; × research-related words; + patient-related words; ● litigation-related words; □ other cancer-related words. 1, diagnosis; 4, positron emission tomography; 5, therapy; 7, radiation therapy; 8, chemotherapy; 9, new drug; 11, surgery or operation; 12, palliative care; 13, home care; 14, end of life or hospice; 15, side effect; 16, complication; 18, cigarette, tobacco, or smoking; 19, prevention; 20, preventive examination; 21, policy; 22, disparity; 24, Basic Act on Cancer Management; 31, medical society; 35, board certified physician; 37, development; 38, clinical trial; 46, genetics; 48, epidemiology; 50, patient's wish; 54, advocacy; 55, litigation or lawsuits; 56, court case; 57, medical accident or medical error; 59, National Cancer Center; 60, Ministry of Health, Labour and Welfare; 61, Ministry of Education, Culture, Sports, Science and Technology.

"Basic Act on Cancer Management," legislation passed in 2006, likely contributed to the appearance of these words. Our study revealed that the appearance of each keyword in the newspapers was influenced by governmental policies, courts, or medical incidents in each period.

Our study showed that cancer is a major topic in newspapers. Information on cancer in newspapers is affected by contemporary politics and incidents. Physicians should be aware of the distinctive characteristics of newspapers, and use them to deliver accurate information to the public.

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The author(s) indicated no potential conflicts of interest.

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CORRESPONDENCE

Cooperative Relationship Between Pharmaceutical Companies, Academia, and Media Explains Sharp Decrease in Frequency of Pulmonary Complications After Bortezomib in Japan

TO THE EDITOR: Bortezomib (Velcade; Millenium Pharmaceuticals, Cambridge, MA) is a promising new drug for multiple myeloma that was approved by the US Food and Drug Administration in May 2003. Japan lags behind Europe and the United States in the release of new drugs. There, unapproved, privately imported bortezomib was administrated without clinical trials until December 2006, when it was approved and released.[1,2]

In October 2005, it became clear that patients who were administered bortezomib before approval in Japan had fatal pulmonary complications.[3] This was 14 months before bortezomib received approval from the Ministry of Health, Labor and Welfare and appeared on the open market in Japan. At that time, there were few reports about severe pulmonary complications with bortezomib in Europe and the United States.[4,5] Medical staff did not recognize that bortezomib might be causing severe pulmonary complications in some patients. By reading reports, medical staff involved in caring for these patients realized the reason for these complications and took measures to reduce the adverse effects. In consequence, it became clear that the frequency of pulmonary complications that occurred before bortezomib became commercially available was dramatically decreased when these adverse effects were reported in the interim report of the postmarketing clinical trial that had been recently disclosed publicly.

Information about how the adverse effects of bortezomib were overcome in a short period will prove to be useful in assessing adverse effects of other new drugs. But in the case in question, additional details about the process are still not known. To investigate the frequency of and reasons for pulmonary complications, we reviewed scientific articlespapers, Web-based information from societies and pharmaceutical companies, newspaper reports, and assessment reports from the Pharmaceuticals and Medical Devices Agency (PMDA). We examined information dating from October 2003, when pulmonary complications were first discovered, to December 2007, when the intermediate results of postmarketing clinical tests were reported. We also interviewed the concerned parties (Fig 1).

Clinical trials of bortezomib as the sole treatment for multiple myeloma patients were started in Japan by Janssen Pharmaceutical Corp in May 2004. Registration of patients was stopped because one patient died as a result of pulmonary complications after bortezomib administration. As a result of meetings held by a third-party evaluation committee, patients with lung problems seen on imaging tests such as a computed tomography were excluded from the clinical trial. Registration of patients was then resumed.[6] Finally, thirty-four patients were registered at the clinical trial; only one (3%) had pulmonary complications. Corticosteroids were not administered in combination with bortezomib to any of the patients. Almost all the patients whose Karnofsky performance status was > 80% were in better health[7] compared with patients who received privately imported bortezomib (Table 1). This information had not been reported by the media until it was made available on Janssen's Web site in October 2005.

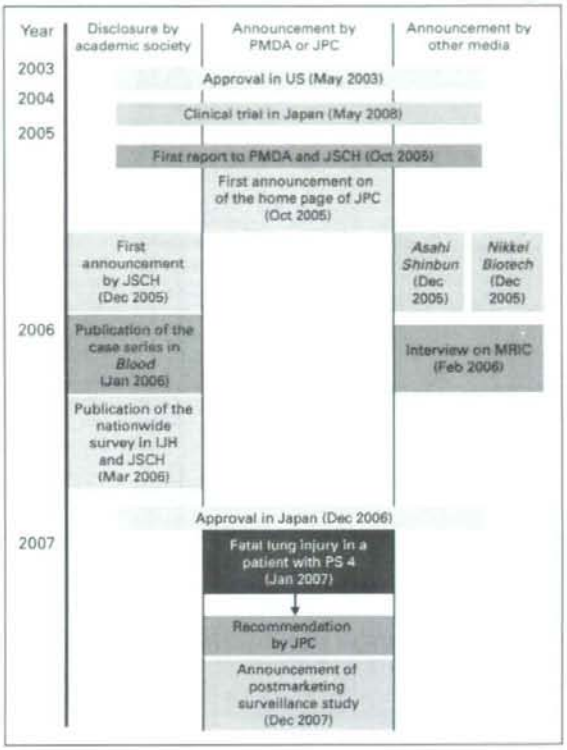

Fig 1. Disclosure of the information on lung injury after bortezomib in Japanese patients. PMDA, Pharmaceutical and Medical Devise Agency; JPC, Janssen Pharmaceutical Corp; JSCH, Japanese Society of Clinical Hematology; IJH, *International Journal of Hematology*; JJCH, *Japanese Journal of Clinical Hematology (Rinshoketsueki)*; PS, performance status.

In October 2005, Miyakoshi et al suspected that bortezomib was the cause of the pulmonary complications because of their experience administering bortezomib to patients who later suffered from pulmonary complications. Miyakoshi contacted colleagues and researchers and learned that similar cases often occurred (S. Miyakoshi, personal communication, June 2008). Miyakoshi's research group investigated medical records from 13 patients who were administered bortezomib that was imported between January 2004 and September 2005.[3] Four patients (31%) had severe pulmonary complications and two of them (14%) died (Table 1). Four patients who had pulmonary complications were not given corticosteroids at the same time. Performance

Table 1. Reports of Severe Pulmonary Complications after Bortezomib Treatment

Parameter	Reports			
	Premarketing Clinical Trial by Janssen Pharmaceutical Corp	Clinical Report by Miyakoshi et al	Nationwide Surveillance by the Japanese Society of Haematology and the Japanese Society of Clinical Haematology*	Postmarketing Surveillance Study (Preliminary Results) by Janssen Pharmaceutical Corp
Study periods	May 2004 to March 2006	June 2004 and September 2005	June 2003 to July 2005	December 2006 to November 2007
Date of public announcement	October 14, 2005 (via Internet)	January 12, 2006 (as *Blood* First Edition article)	March 20, 2006 (via Internet and the official journals)	December 26, 2007 (via Internet)
No. of enrolled patients	34	13	46	666
Karnofsky performance status	All the patients are ≥ 60 (97% of the patients are ≥ 80)	NA		NA
Median			70	
Range			20-100	
Patients who received concomitant corticosteroid treatment				
No.	0	NA (4 patients with pulmonary complication did not receive steroids)	25	124
%	0		54	70
Patients who developed pulmonary complication				
No.	1	4	7	24
%	3	31	15	3.6
Patients with fatal pulmonary complication				
No.	1	2	3	4
%	3	14	7	0.5

Abbreviation: NA, not available.
*Included the 13 patients who had been reported by Miyakoshi et al.
†One hundred seventy-eight patients were evaluable.

status (PS; Eastern Cooperative Oncology Group) in these four patients and clinical information for nine patients who had no pulmonary complications were not available. In October 2005, Miyakoshi et al sent the first report about the possibility of pulmonary complications with bortezomib to PMDA, Janssen, and a company that imports bortezomib (RHC USA Corp, Honolulu, HI). PMDA asked Jansses to issue announcements to patients who took part in the clinical trial and to medical staff about the severe pulmonary complications with bortezomib. In the past, information about adverse effects in patients who took part in clinical trials had not been made available except to the hospital that took part in the clinical trial. This time, Jansses showed this information on its Web site on October 24th, 2007, in compliance with PMDA's request. RHC USA Corp wrote letters to doctors on October 25th, 2005, providing them with the information. Miyakoshi et al. submitted this result to *Blood* on November 16th, 2005, and posted it online on January 12th, 2006.[3] Miyakoshi pointed out the problem of information disclosure related to private medicine importing during an online interview.[8] In August and November 2006, American hospitals reported that African Americans had the same severe pulmonary complications with bortezomib.[9,10]

The Japanese Society of Hematology and the Japanese Society of Clinical Hematology together surveyed self-reported pulmonary complications on a nationwide scale in November 2005. They showed the results on their Web sites on December 6th, 2005. The results were reported in the *Asahi Shimbun* newspaper on December 11th, and in *Nikkei Biotech* on December 19th. Final results of the investigation were shown on both societies' Web sites on March 20th, 2006, and were also shown in both societies' academic journals.[1,2] A total of 46 patients were administered imported bortezomib from January 2003 to July 2005. Their median Karnofsky PS was 70% (range, 20% to 100%).[11] Seven (15%) had pulmonary complications, and three (6.5%) died. Twenty-five (54%) were administered corticosteroids with bortezomib and experienced significantly decreased frequency of pulmonary complications.[1]

Bortezomib was approved by the Ministry of Health, Labor and Welfare on October 2006, and sales began on the open market in December 2006. After being requested to investigate usage results for all patients, Janssen set a proper usage criterion and recommended that doctors withhold administration of bortezomib from patients whose Karnofsky PS was < 60 and who had interstitial lesions on their chest radiographs. It came to light in January 2007 that two patients with PS 4 who were administered bortezomib had died of pulmonary complications.[12] This was discussed at a third-party evaluation committee headed by Jansses, after which the corporation strongly recommended that doctors not use bortezomib for PS 3 or PS 4

patients. Intermediate results of postmarketing clinical tests performed in 666 patients who were administered bortezomib after it came to market in November 2007 were reported on Janssen's Web site in December 2007. Twenty-four (3.6%) had pulmonary complications, and three (0.5%) died (Table 1).[13] Information about PS has not been made available to the public. It came into the open in a May 2008 Janssen lecture delivered in Tokyo to commemorate the sale of Velcade that corticosteroids were administered with bortezomib to almost 70% of patients. The drug manufacturer in the United States showed pulmonary complications for Asians in the product document of bortezomib in May 2006.[14]

Compared with the period when bortezomib was being imported by doctors, the frequency and lethality rate of pulmonary complications at the postmarketing clinical trial decreased. We think some possible causes for this are as follows: first, combined administration with corticosteroids became popular. Fifty-four percent of patients who were administered imported bortezomib were also administered a steroid in combination.[3,6] This frequency increased to 70% at the postmarketing clinical trial. The steroid has an antitumor effect on multiple myeloma and is used with many kinds of medicine. Gotoh et al[1,2] showed that the risk of pulmonary complications decreased with a combination of bortezomib and the steroid. As a result of this study, some doctors might begin using bortezomib in combination with the steroid for preventing pulmonary complications. Second, as reports of pulmonary complications with bortezomib increased, some doctors began to choose patients carefully. During the clinical trial, Miyakoshi et al found that pulmonary complications occurred in succession with patients in poor general condition who were administered an unapproved drug. After bortezomib went on the market, Janssen set a proper usage criterion that included lung disease history and Karnofsky PS, and the company thoroughly educated doctors. This probably contributed widely to the decrease in adverse events in postmarketing clinical trials.

In this case, the period between the discovery of pulmonary complications with bortezomib and the adoption of countermeasures was short. It took only 14 months from the discovery of possible pulmonary complications with bortezomib by Miyakoshi et al to the start of the postmarketing clinical test. During this period, strong measures to reduce the pulmonary complications were taken in clinical practice, as presented in this article. The case highlights some interesting points regarding the communication of medical information. Miyakoshi, who first realized the complications, called and sent e-mails directly to neighborhood hospitals to inquire about this. This shows that doctors can exchange information easily because of the widespread use of information technology. It would have taken much longer for doctors to realize the problem of pulmonary complications with bortezomib without the advantage of information technology. In addition, Miyakoshi et al promptly communicated the risk of adverse effects to the PMDA, Janssen, academic societies, and import agencies. In Japan, a system for collecting information on adverse events related to unapproved drugs has not been established.[15] In this case, however, the information was transmitted to doctors comprehensively and promptly because Miyakoshi et al shared their finding of adverse effects related to bortezomib with several organizations, each of which disclosed the information in their own way.

Various media reported this problem at an early stage. Mass media such as the *Asahi Shinbun* newspaper reported that not only medical staff but also patients and their families recognized the adverse effects of bortezomib. When we think about broadcasting information to the nation, it is necessary to work together with the mass media and medical community, and we should consider the special qualities of each form of media in order to provide information effectively and efficiently. It has been shown in previous situations that mass media such as newspapers can distribute information to many people, but there is a possibility that the information may be incomplete or inaccurate.[16] However, although they are targeted only at medical professionals, industry publications such as Medical Research Information Center and *Nikkei Biotech* can provide more accurate and detailed information in a way that cuts across disciplinary divisions in the world of specialized medicine. In this case, different types of media supplied information concerning pulmonary complications with bortezomib through journals and academic societies, and the risk became widely known in a very short time.

The information about pulmonary complications with bortezomib was shared with concerned parties in a short time, and administration of bortezomib was optimized. In this process, in addition to academic societies and pharmaceutical companies, the mass media, use of e-mail, and the Internet played a stronger role.

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Pleomorphic Lobular Carcinoma of the Breast: Four Long-Term Responders to Trastuzumab—Coincidence or Hint?

To the Editor: Positivity for human growth factor receptor 2 (HER-2) occurs in 20% to 25% of all invasive breast cancers. Infiltrating lobular carcinomas—another relatively uncommon entity—constitute only 7% to 10% of all invasive breast cancers. The pleomorphic lobular carcinoma (PLC) variant accounts for approximately 15% of all invasive lobular carcinomas.[1,2] In general, lobular carcinomas are rarely HER-2 positive (8% per Gonzalez-Angulo et al[3]). In contrast, at least 30% of instances of PLC are identified HER-2 positive by fluorescence in situ hybridization (FISH).[4,5] Thus, HER-2–positive PLC should constitute an extremely rare subtype of invasive breast cancers.

We describe four patients with PLC who appear to have exquisite sensitivity to trastuzumab. The first patient had a mastectomy for a 7-cm, node-positive, HER-2–positive by FISH, hormone receptor–positive tumor. She was treated with adjuvant chemotherapy and hormonal therapy, but developed biopsy-proved liver metastases 3 years later. She continues to receive trastuzumab at 9 years, with no evidence of recurrent disease. The second patient presented with severe inflammatory carcinoma, and was treated with paclitaxel and trastuzumab, with complete pathologic response in the breast and lymph nodes. She completed 1 year of adjuvant trastuzmab, along with radiation therapy to the left chest wall and draining lymphatics, and has been disease free for 8 years. She did develop a new early-stage primary lung cancer that was treated surgically. The third patient had a primary breast cancer that was treated with mastectomy. Bone metastases were diagnosed shortly after completion of adjuvant chemotherapy. She was treated with capecitabine and trastuzumab for 1.5 years. The capecitabine was then discontinued, and her disease has been totally controlled with the administration of trastuzumab alone for 9 years, with bone imaging demonstrating a few residual sclerotic lesions. The fourth patient had a mastectomy for a 4-cm, node-negative, HER-2–positive by FISH, hormone receptor–positive tumor characterized as a grade 2 infiltrating lobular carcinoma. According to our local pathologist, this tumor may have been termed a PLC with an older classification system. She was given adjuvant chemotherapy, and biopsy-proved bone metastases were diagnosed 2 years later. Treatment included vinorelbine and trastuzumab for 1 month, followed by single-agent trastuzumab for 4 years, with no evidence of metabolically active metastatic disease on most recent imaging.

Although these four patients may represent a remarkable coincidence, they may instead provide a hint of extreme sensitivity to trastuzumab within this rare subset of patients. We present these patients to suggest that others seek similar associations, which, if present, could stimulate gene microarray studies aimed at finding commonalities within this small group of patients.

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