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Int J Clin Oncol (2012) 17:533
DOI 10.1007/s10147-012-0495-4

INTRODUCTION TO REVIEW ARTICLES

Drug-induced interstitial lung disease (DILD) in molecular targeted therapy

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Received: 26 October 2012 / Published online: 15 November 2012

The development of molecularly targeted agents has been a key factor in recent advances in cancer therapy, and some of these agents are now considered standard therapies for various types of carcinoma. The toxicity of molecularly targeted agents is different from that of cytotoxic antitumor agents. ILD in Japanese patients treated with molecular targeting agents has been the focus of many studies.

Among tyrosine kinase inhibitors, gefitinib and erlotinib are associated with an increase in the incidence of ILD in Japanese patients. Gefitinib-induced DLI was reported to be 3.5 % in a retrospective analysis and 5.8 % in a prospective study of Japanese patients with non-small-cell lung cancer (NSCLC). In a cohort study including gefitinib and chemotherapy in Japanese patients with NSCLC, the naive cumulative incidence rates at the end of 12-week follow-up were 4.0 % for gefitinib versus 2.1 % for conventional chemotherapy.

Little was known about drug-induced ILD when acute ILD-type events developed in Japanese patients treated with molecularly targeted agents including gefitinib. A better understanding of drug-induced ILD is required, including more reliable data about the incidence of events associated with different treatments and identification of the risk factors for this type of ILD. Recent advances in imaging, molecular examination, and pathology have been used in postmarketing surveillance studies designed and conducted by an independent academic team to define the risk and to increase the amount of evidence about ILD related to various molecularly targeted anticancer agents. The present analysis provides useful information about ILD to health-care professionals involved in treatment using molecular targeted therapy. These studies may shed light on the underlying mechanisms of drug-induced ILD and appropriate evidence-based strategies that can be used to prevent or manage these events. At this time, information about ILD by these molecular targeted agents including anti-EGFR antibodies, mTOR inhibitors, bortezomib, and multi-kinase inhibitors has accumulated. The difference in ILD according to causative drugs has been clarified. As for the treatment of DILD, the general rule is the discontinuation of the offending drug, and, if necessary, the administration of corticosteroids is indicated. However, exceptional treatment is required for DILD caused by mTOR inhibitor, for which we must consider adequate management. Based on this information, the guideline for drug-induced ILD was revised by the Japanese Respiratory Society this year.

In this issue, two experts describe the most recent findings from internal medicine and radiology in this field. We hope that these review articles will be helpful for understanding DILD in molecular targeted therapy.

Conflict of interest Akihiko Gemma is receiving a research grant from Pfizer Inc.; Akihiko Gemma has received lecture fees from Chugai Pharmaceutical Co., Ltd., Novartis Pharma K.K., Pfizer Inc., and Bayer Yakuhin, Ltd.

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Int J Clin Oncol (2012) 17:534–541
DOI 10.1007/s10147-012-0494-5

REVIEW ARTICLE

Current status of DILD in molecular targeted therapies

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Received: 21 October 2012 / Published online: 15 November 2012

Abstract Molecular targeted drugs have become the mainstream for cancer therapy, and they have contributed to improving the outcome for cancer patients. On the other hand, molecular targeted drugs are associated with a variety of adverse drug reactions. Drug-induced interstitial lung disease (DILD) is a typical adverse drug reaction that has been an important problem with regard to safety management during cancer treatment. In the past, there was a lack of detailed and accurate epidemiological data about DILD. However, most of the molecular targeted drugs have been subject to all-case post-marketing surveillance since gefitinib-induced ILD became a concern. These surveillance data present useful information about DILD, such as frequency of adverse events, mortality, and risk factors, and as a result, the epidemiological profile of DILD associated with molecular targeted drugs has become apparent during the past decade. Further, it has been considered that the principal management for DILD is early detection and cessation of the suspected cause. However, ILD associated with everolimus and temsirolimus requires unusual management; i.e., patients with asymptomatic ILD are allowed to continue treatment with everolimus or temsirolimus, and even after symptomatic ILD, both everolimus and temsirolimus are allowed to be readministered after the resolution of ILD. As a result of the collected data, a change has begun in the field of DILD associated with molecular targeted drugs. The features of DILD can differ for each drug, and clinicians should thus keep this information about DILD in mind while treating patients.

Keywords Drug-induced interstitial lung disease · Molecular targeted drug · Epidemiology · Management

Introduction

A number of drugs have the potential to cause drug-induced interstitial lung disease (DILD). Anticancer drugs are thought to be the most common drugs that induce ILD, and the proportion of molecular targeted drugs that cause the condition appears to be relatively high. Gefitinib, which was the first molecular targeted drug approved for non-small cell lung cancer (NSCLC), was launched in Japan 10 years ago, with the expectation that it would be an easy-to-use anticancer drug. Many patients received gefitinib soon after its launch. However, numerous cases of acute lung injury or interstitial pneumonia were soon reported. Some of these cases were fatal, and as a result, gefitinib-induced ILD generated a social problem. This experience influenced the safety management of drugs. For instance, when pharmaceutical companies launched new anticancer drugs, they began to conduct large-scale post-marketing surveillance (PMS) studies, such as all-case surveillance, to collect accurate and sufficient safety data from a larger population.

The development of molecular targeted drugs has been remarkable during the past decade, and more than 20 molecular targeted drugs are currently available in Japan. The epidemiology of drug-induced ILD as cancer therapy with molecular targeted drugs has been demonstrated through the PMS data, and various aspects of ILD, such as frequency and prognosis, differ among the drugs. In this

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article, the current status of ILD associated with molecular targeted drugs in cancer patients is described.

Molecular targeted drugs and safety measures for DILD in Japan

Table 1 lists the molecular targeted drugs that are approved in Japan. These drugs are used for various types of tumors, and all the drugs have the potential to induce ILD to varying degrees. Thus, physicians in various specialties, other than respiratory specialists, have the potential to encounter an ILD, and this also generates concern about appropriate management for ILD in all situations involving therapy with molecular targeted drugs. When a new drug is launched, specific requirements for physicians and medical institutions are often defined to safely conduct treatment for cancer (e.g., the physician must be familiar with the cancer therapy, and the medical institution must be able to perform sufficient safety management for the patients in the case of an emergency.). For example, physicians may be required to participate in "e-learning" before using erlotinib for patients with pancreatic cancer. For drugs with a certain level of risk, as in the case of erlotinib, strengthening of such regulations may be implemented in the future.

Detailed information about ILD regarding each drug is needed and would be helpful for physicians. Recently, the pharmaceutical industry has begun to provide guidebooks for the proper use of drugs for physicians, reminding them about the possibility of important adverse drug reactions, including ILD. In addition, almost all the molecular targeted drugs launched after the incidents involving gefitinib-induced ILD have been subjected to all-case surveillance studies (Table 1). The final analysis reports or interim analysis reports of the all-case surveillance studies have been published for some of these drugs, and these results provide accurate epidemiological data about ILD.

Table 1 Molecular targeted drugs used in Japan

Year approved	Drug	Indication(s)	All-case surveillance
1995	Tretinoin	Acute promyelocytic leukemia	−
2001	Rituximab	CD20-positive B-cell non-Hodgkin's lymphoma	−
	Trastuzumab	HER2-overexpressing breast cancer and gastric cancer	−
	Imatinib	Chronic myeloid leukemia, KIT (CD117)-positive gastrointestinal stromal tumors, Philadelphia chromosome-positive acute lymphoblastic leukemia, FIP1L1-PDGFRα-positive hypereosinophilic syndrome, and chronic eosinophilic leukemia	−
2002	Gefitinib	EGFR gene mutation-positive non-small cell lung cancer	−
2005	Tamibarotene	Acute promyelocytic leukemia	+
	Gemtuzumab ozogamicin	CD33-positive acute myeloid leukemia	+
2006	Bortezomib	Multiple myeloma	+
2007	Bevacizumab	Colorectal cancer, non-squamous non-small cell lung cancer, breast cancer	+
	Erlotinib	Non-small cell lung cancer, pancreatic cancer	+
2008	Ibritumomab	CD20-positive B-cell non-Hodgkin's lymphoma and mantle cell lymphoma	+
	Sorafenib	Renal cell carcinoma, hepatocellular carcinoma	+
	Sunitinib	Imatinib-resistant gastrointestinal stromal tumor, renal cell carcinoma, pancreatic neuroendocrine tumor	+
	Cetuximab	EGFR-expressing colorectal cancer	+
	Thalidomide	Multiple myeloma	+
2009	Dasatinib	Chronic myeloid leukemia, Philadelphia chromosome-positive acute lymphoblastic leukemia	+
	Nilotinib	Chronic myeloid leukemia	+
	Lapatinib	HER2-overexpressing breast cancer	+
2010	Everolimus	Renal cell carcinoma, pancreatic neuroendocrine tumor	+
	Panitumumab	*KRAS* wild-type colorectal cancer	+
	Lenalidomide	Multiple myeloma, deletion 5q myelodysplastic syndrome	+
	Temsirolimus	Renal cell carcinoma	+
2011	Vorinostat	Cutaneous T-cell lymphoma	+
2012	Crizotinib	ALK-positive non-small cell lung cancer	+
	Axitinib	Renal cell carcinoma	−

The epidemiology of ILD based on these published data, mainly from the analyses of all-case surveillance studies, is described below.

The epidemiology of ILD associated with molecular targeted drugs in Japan

EGFR-TKI (gefitinib and erlotinib)

Gefitinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that was approved for the treatment of NSCLC. Only a few months after the launch of gefitinib, reports of acute lung injury or interstitial pneumonia related to gefitinib therapy started to accumulate and some of the cases had a fatal outcome [1]; then, the "Dear Healthcare Professional" Letter of Emergency Safety Communication (a so-called "Yellow Letter") was released. Although these findings led to a social problem, wherein patients started to be afraid of treatment with the drug, interest in ILD associated with molecular targeted drugs grew, and large-scale studies were conducted to clarify the epidemiology of gefitinib-induced ILD.

The Iressa tablets 250 prospective study was carried out, which included more than 3,000 patients with NSCLC, to clarify the incidence of gefitinib-induced ILD and its risk factors [2]. The frequency of ILD in that study was 5.8 % (193/3,322 cases), based on the comprehensive assessment using each individual case record and X-ray and computed tomography (CT) images by the judging committee, and the mortality rate was 38.9 % (75/193 cases) among all the patients with ILD. Furthermore, a multivariate analysis suggested that there was an increase in the incidence of ILD as follows: (1) cases with a performance status (PS) $\geq$2 [estimated hazard ratio (HR) = 2.15, 95 % confidence interval (CI) 1.44–3.21, $p < 0.01$]; (2) cases with a history of smoking (HR = 1.99, 95 % CI 1.25–3.16, $p < 0.01$); (3) cases complicated with interstitial pneumonia at the time of initial administration of the drug (HR = 2.50, 95 % CI 1.18–5.28, $p = 0.016$); and (4) cases with a history of prior chemotherapy (HR = 1.79, 95 % CI 1.05–3.04, $p = 0.032$). Regarding the factors predicting a poor prognosis (fatal cases), a higher mortality rate was suggested for male patients and cases with a PS $\geq$2.

Additionally, a cohort and nested case-control study was carried out to elucidate the risk factors for ILD in 3,166 Japanese patients with NSCLC during treatment with gefitinib or other chemotherapy [3]. This study revealed that the frequency of ILD was higher in the gefitinib cohort than in the conventional chemotherapy cohort (3.98 vs. 2.09 %). The adjusted overall odds ratio (OR) of developing ILD with gefitinib treatment versus chemotherapy was 3.23 (95 % CI, 1.94–5.40), and the risk of ILD was especially high in the first 4 weeks after the start of treatment. On the other hand, the mortality rate from ILD was not significantly different between gefitinib and chemotherapy cohorts [31.6 vs. 27.9 %; OR, 1.05 (95 % CI, 0.3–3.2) for gefitinib vs. chemotherapy]. The risk factors for ILD in both the gefitinib and chemotherapy groups were identified as follows: older age ($\geq$55 years), WHO PS ($\geq$2), smoking history, short duration since the diagnosis of NSCLC (<6 months), reduced extent of normal lung volume on CT scan (<50 %), preexisting ILD, and concurrent cardiac disease. In addition, the risk factors for a fatal outcome of ILD were age ($\geq$65 years), smoking history, preexisting ILD, CT evidence of a reduced normal lung volume ($\leq$50 %), and/or extensive areas adherent to the pleura ($\geq$50 %).

Erlotinib was approved for NSCLC 5 years after the approval of gefitinib. ILD was reported to occur in 6.5 % (4/62 cases) of Japanese NSCLC patients during a phase II clinical trial of erlotinib [4], and the issue of ILD was of similar concern as with gefitinib. The number of Japanese patients enrolled in the clinical trials was small, so an all-case surveillance study was conducted to elucidate the frequency, prognosis, and risk factors for ILD. The final results of the surveillance revealed that ILD developed in 4.5 % (158/3,488 cases) of the patients, and the mortality rate from ILD was 34.8 % (55/158 cases). ILD developed most often in the first 2 weeks after starting erlotinib therapy and thereafter gradually decreased. A multivariate analysis showed that concomitant or previous ILD, a smoking history, concomitant or previous lung infection, and an Eastern Cooperative Oncology Group PS 2–4 were significant risk factors for the development of ILD [5].

The frequency of and the mortality rate from ILD, and the time period when patients are most likely to develop ILD, are similar for gefitinib and erlotinib. ILD occurs in 4–5 % of patients, and about one third of these cases have a fatal outcome. Although the pathogenesis and pathology of ILD caused by EGFR-TKI are still not fully understood, presentation of a diffuse alveolar damage (DAD) pattern has been demonstrated to be strongly correlated with a fatal outcome [1, 6–9].

Erlotinib, intended for concomitant use with gemcitabine, was recently approved for the treatment of pancreatic cancer. In a phase II clinical trial of erlotinib plus gemcitabine for Japanese pancreatic cancer patients, ILD developed in 8.5 % (9/106 cases) of the patients in the erlotinib plus gemcitabine group [10]. Fortunately, there were no fatalities in these patients with ILD; however, the frequency of ILD was higher than that in NSCLC patients treated with erlotinib alone. All-case surveillance is still ongoing for safety monitoring.

Anti-EGFR monoclonal antibodies (cetuximab and panitumumab)

Cetuximab was approved for EGFR-positive colorectal cancer, and is often used with irinotecan or FOLFIRI. All-case surveillance of cetuximab has been completed; the final results showed that the frequency of ILD was 1.2 % (24/2,006 cases), and 10 of the 24 patients with ILD died. The median time to onset of ILD was 101 days (range, 17–431 days), and no particular tendency with regard to the time to onset of ILD was suggested [11].

Panitumumab was approved for *KRAS* wild-type colorectal cancer, and as with cetuximab, it is used in combination with other cytotoxic drugs, including FOLFOX and FOLFIRI, or can be used as monotherapy. An interim analysis of the all-case surveillance of panitumumab showed that the frequency of ILD was 1.1 % (19/1,767 cases), and the frequency of ILD in the subgroups of patients receiving panitumumab monotherapy, in combination with FOLFOX, and in combination with FOLFIRI were 1.0, 1.4, and 1.3, respectively. Regarding mortality from ILD, at least 7 of 19 ILD cases were fatal (5 cases are still under investigation) [12].

Both cetuximab and panitumumab target EGFR signaling, the same as EGFR-TKI; however, the incidence of ILD resulting from anti-EGFR monoclonal antibody therapy seems to be lower than that caused by EGFR-TKI therapy. On the other hand, the mortality rate from ILD is similar for anti-EGFR monoclonal antibodies and EGFR-TKI.

Bevacizumab

Bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, was approved for the treatment of colorectal cancer and non-squamous NSCLC. All-case surveillance was conducted for patients with colorectal cancer, and most of these patients were treated with a combination of bevacizumab and FOLFOX or FOLFIRI. The final results of the surveillance study showed that the frequency of ILD was 0.37 % (10/2,698 cases), and the mortality rate from ILD was 20 % (2/10 cases). In addition to ILD, acute respiratory distress syndrome (ARDS) was reported in 0.15 % (4/2,698 cases) of the patients, and 3 of 4 patients with ARDS died [13].

Bortezomib

Bortezomib is a proteasome inhibitor that was approved for multiple myeloma. Before to the approval of bortezomib in Japan, severe pulmonary complications were reported in patients with multiple myeloma who were treated with the drug, which raised safety concerns about bortezomib therapy [14]. These patients had been treated with bortezomib that had been imported by the attending physicians at the patients' request. Four of 13 patients developed pulmonary complications, and 2 of the patients died. One of the 2 fatal cases was diagnosed with DAD by autopsy. Thereafter, the Japanese Society of Hematology and the Japanese Society of Clinical Hematology performed a cooperative survey by questionnaire to assess the pulmonary complications associated with bortezomib [15]. The frequency of pulmonary complications was 15.2 % (7/46 cases), and 3 of 7 patients with pulmonary complications died during that surveillance period. A multivariate analysis suggested that a prior history of stem cell transplantation could be a risk factor for the development of ILD. On the other hand, it was suggested that concomitant use of corticosteroids may reduce the risk of developing ILD.

After the official launch of bortezomib, all-case surveillance was conducted; the final results showed that the frequency of pulmonary complications (including lung injury, interstitial pneumonia, hypoxemia, oxygen desaturation, non-cardiogenic pulmonary edema, and capillary leak syndrome) was 3.77 % (31/823 cases), and the mortality rate from pulmonary complications was 6.5 % (2/31 cases) [16]. The frequency of pulmonary complications in the post-marketing surveillance data was lower than that during the previous surveillance data, and the reason why the pulmonary complications decreased after the launch was considered to be that patients with a worse PS were considered to be contraindicated for treatment with bortezomib, and that there was a higher proportion of concomitant use of corticosteroids after the launch of bortezomib [16].

Sorafenib and sunitinib

Sorafenib is a multi-kinase inhibitor that targets Raf kinase and receptor tyrosine kinases, including the VEGF receptor and platelet-derived growth factor receptor (PDGFR). Sorafenib was approved for the treatment of renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC). The analysis of ILD in the all-case surveillance for RCC and HCC showed that the frequency of ILD in these studies was 0.33 % (8/2,407 cases) and 0.62 % (4/647 cases), respectively, and 50 % of patients with ILD died [17]. This study also showed that 62 patients with ILD were identified among approximately 13,600 sorafenib-treated patients through the PMS. Chest CT scans were available for 33 patients with ILD and were evaluated by experts: a DAD pattern was identified in 18 of the 33 patients. Although sorafenib-induced ILD may occur less frequently than ILD from other agents, the mortality rate seems to be considerably higher.

Sunitinib is another multi-kinase inhibitor that targets receptor tyrosine kinases including VEGF, PDGF, KIT, FLT3, CSF-1R, and RET. Sorafenib was approved for imatinib-resistant gastrointestinal stromal tumors (GIST), RCC, and pancreatic neuroendocrine tumors (PNET). The final results of the all-case surveillance for GIST and RCC showed that the frequency of ILD was 0.65 % (14/2,141 cases) and that 3 of the 14 patients with ILD died [18].

Dasatinib and nilotinib

Both dasatinib and nilotinib are second-generation Bcr-Abl TKI. Dasatinib was approved for chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL). An interim report of the all-case surveillance showed that the frequency of ILD was 2.9 % (24/838 cases). The mortality was unclear, but 12 of the 24 patients with ILD had ≥grade 3 status [19].

Nilotinib was approved for CML. The interim report of all-case surveillance showed that the frequency of ILD was 1.4 % (9/629 cases) and 2 of the 9 patients with ILD died [20]. ILD generally developed within the first 2 weeks after starting the therapy and was more common in male and elderly patients.

Imatinib

Imatinib is a TKI that targets Bcr-Abl, KIT, and PDGF receptor tyrosine kinases. Imatinib was approved for the treatment of CML, KIT (CD117)-positive gastrointestinal stromal tumors, Philadelphia chromosome-positive ALL, FIP1L1-PDGFRα-positive hypereosinophilic syndrome, and chronic eosinophilic leukemia. All-case surveillance was not conducted; however, an article appeared regarding imatinib-related ILD in Japanese patients with CML and GIST [21]. In this article, 27 cases of imatinib-related ILD were evaluated in detail. The chest CT findings presented various patterns, but the DAD pattern was not identified. Of the 27 cases, 24 were treated with corticosteroids and 3 cases were not treated (only discontinuation of imatinib); most of the cases were improved or recovered, without a fatal outcome. Although the actual incidence of imatinib-related ILD is unclear, the prognosis seems to be favorable.

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin is a CD33 monoclonal antibody combined with the cytotoxic drug calicheamicin. Gemtuzumab ozogamicin was approved for CD33-positive acute myeloid leukemia. All-case surveillance showed that the frequency of ILD (including ARDS and acute lung injury) was 1.6 % (12/753 cases), and 4 of 12 patients with ILD died [22].

Lapatinib

Lapatinib is a TKI that targets the EGFR and HER2. Lapatinib was approved for HER2-overexpressing breast cancer. An interim report of all-case surveillance showed that the frequency of ILD was 0.5 % (11/2,201 cases), and 1 of 11 patients with ILD died [23].

mTOR inhibitors (everolimus and temsirolimus)

Both everolimus and temsirolimus are mammalian target of rapamycin (mTOR) inhibitors. Everolimus was approved for RCC and PNET as an anticancer drug (AFINITOR). It was also approved as an immunosuppressant for the prevention of allograft rejections of heart and kidney transplants (CERTICAN). ILD developed at a high frequency in the phase III clinical trials of everolimus for RCC and PNET (13.5 and 17.2 %, respectively) [24, 25]. An interim report of the all-case surveillance showed that the frequency of ILD was 17.4 % (105/605 cases) and the mortality rate from ILD was 3.8 % (4/105 cases). It should be noted that about 30 % of the patients with ILD were asymptomatic.

Although a high frequency of everolimus-induced ILD was reported in cancer trials, the development of ILD is relatively rare when everolimus is used as an immunosuppressant (the frequency of ILD is indicated to be 0.3 % in the package insert for CERTICAN). It is unclear why the frequency of ILD is lower for CERTICAN. However, it is possible that the difference in the dose of everolimus (10 mg/day for AFINITOR, 3 mg/day for CERTICAN) and concomitant use of corticosteroid and other immunosuppressants, such as cyclosporine, may be responsible for the difference.

Temsirolimus was approved for RCC. Temsirolimus also leads to the development of ILD. All-case surveillance is currently ongoing, and conclusive data have not yet been published. A phase III clinical trial of temsirolimus for RCC indicated that the frequency of ILD was 2 % (4/208 cases) [26]. However, retrospective analyses of the chest CT scans by specialists identified more ILD than did the investigators in the clinical trial, and the frequency of ILD increased to 29 % [27]. A similar result was obtained with regard to everolimus-induced ILD [24]. That is, although the frequency of ILD was 13.5 % in the report by the investigators of the clinical trial, during the retrospective review by specialists, new or worsening radiographic changes related to pneumonitis were observed in 53.9 % of the patients receiving everolimus. These results indicate

that some of the cases of ILD, such as asymptomatic cases, may be missed during the treatment with mTOR inhibitors.

It should be noted that mTOR inhibitors have an immunosuppressive effect and may lead to the development of opportunistic infections. Pneumocystis pneumonia (PCP) is the most important opportunistic pulmonary infection, because it is difficult to distinguish ILD and PCP as the chest images have similarities, and this can lead to a misdiagnosis. Therefore, clinicians should keep PCP in mind as a differential diagnosis.

Management for ILD

Diagnosis and management

It is sometimes difficult to make a definitive diagnosis of DILD because there are no specific biomarkers, radiographic findings, or pathological patterns for DILD. The diagnostic criteria are currently considered to be the following: (1) there should be a history of drug exposure; (2) the clinical, imaging, and pathological pattern of lung involvement should conform to earlier observations with the drug; (3) the etiology of lung disease(s) other than ILD should be ruled out; (4) improvement should follow discontinuation of the suspected drug; and (5) symptoms should recur upon re-challenge [28]. The most important point is to provide an exclusive diagnosis. The differential diagnosis for DILD includes infectious diseases, cancer progression (e.g., lymphangitic carcinomatosis), congestive heart failure, pulmonary embolism/infarction, preexisting interstitial pneumonia, and radiation pneumonitis. Combinations of blood examinations, radiologic imaging, bacterial culture, and bronchoscopic examination are useful for obtaining the differential diagnosis. Appropriate evaluations of these examinations therefore require close cooperation with respiratory specialists.

The principle of management for DILD is early detection and cessation of treatment with the suspected drug. Education of patients about DILD may be helpful for early detection and may affect the prognosis of ILD. Discontinuation of the suspected drug alone may improve mild cases of ILD, and when the symptoms do not improve by discontinuation of the drug, or when the cases are severe, the administration of corticosteroids is recommended.

The response to corticosteroid therapy depends on the pathological pattern of ILD. DILD presents a broad spectrum of histopathological patterns, including DAD, nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), eosinophilic pneumonia (EP), and hypersensitivity pneumonia (HP) [29]. Among them, patients with the OP, EP, and HP patterns are expected to show a good response to

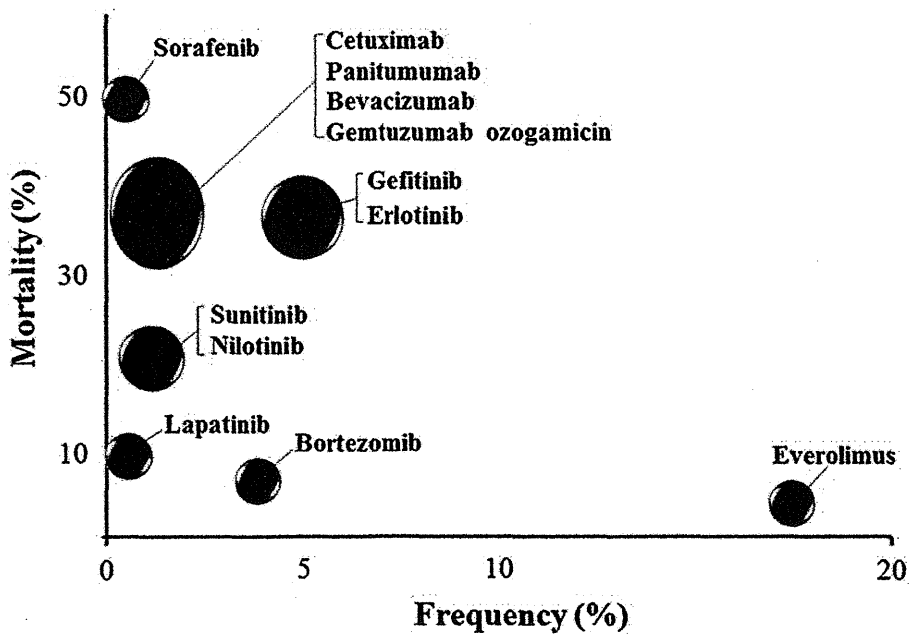

Fig. 1 A diagram showing the relationship between the frequency and the prognosis of drug-induced interstitial lung disease (DILD). The *horizontal axis* and the *vertical axis* show the frequency of interstitial lung disease (ILD) and the mortality rate from ILD, respectively. The data are based on the final or interim analyses of all-case surveillances available as of October 2012. For gefitinib, the data from the *Reports on Iressa Tablets 250 prospective study (special investigation)* were utilized

corticosteroid therapy; however, DAD is usually refractory to corticosteroid therapy and often becomes fatal. There is no established therapy for ILD that is refractory to corticosteroid therapy.

The prognosis of the DILD is considered to vary depending on the frequency of the DAD pattern. Thus, it is important to determine whether the presenting ILD has a DAD pattern. A histopathological examination is needed for the diagnosis. However, the patient often presents in serious condition and it is difficult to perform a lung biopsy in these patients. In such situations, high-resolution computed tomography is helpful to estimate the pattern of ILD.

In general, the suspected drug should be immediately discontinued, and readministration should be avoided. In contrast, the management policy for ILD associated with everolimus or temsirolimus differs from the conventional policy. There are two significant aspects of the management for ILD associated with mTOR inhibitors: (1) in the cases of ILD without symptoms (grade 1), continuing cancer therapy with everolimus is allowed; (2) in cases of symptomatic ILD with severity of grade 2 or 3, everolimus should be discontinued, but after the resolution of ILD, everolimus can be administered again if the benefit–risk balance is considered to be favorable [30]. Temsirolimus-induced ILD is managed in a similar manner [31].

Conclusion

Little was known about the epidemiology of DILD in the past. However, beginning with the documentation of acute lung injury and interstitial pneumonia associated with gefitinib therapy, large-scale PMS data regarding DILD have been accumulated in the past decade. The characteristic features of DILD associated with molecular targeted drugs and their relationship with the frequency of ILD and the mortality from ILD are shown in Fig. 1. The diagram indicates that the frequency and the prognosis of DILD vary by drug. The risk factors for DILD have been analyzed for some drugs. For example, gefitinib and erlotinib tend to lead to the development of ILD in patients with a poor PS, preexisting lung disease, and a smoking history. These epidemiological data and analyzed risk factors are useful for determining the proper indications for treatment using molecular targeted drugs, and it may be possible to ensure a favorable benefit–risk balance for these drugs by deciding on the indications for these drugs after taking into consideration the risk factors for ILD.

Conflict of interest Yoshinobu Saito has no conflict of interest. Akihiko Gemma is receiving a research grant from Pfizer Inc. Akihiko Gemma has received lecture fees from Chugai Pharmaceutical Co. Ltd, Novartis Pharma K.K., Pfizer Inc., and Bayer Yakuhin Ltd.

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≪小細胞肺癌治療の考え方と実践≫
二次治療のエビデンス

石黒　敦　西條康夫*

要旨

- 小細胞肺癌に対する初回導入化学療法として cisplatin＋irinotecan，あるいは cisplatin＋etoposide による併用療法 4 コースが標準であり，維持化学療法は行われない．
- 再発小細胞肺癌の二次治療に際しては初回治療終了後から再発までの期間が重要であり，再発部位，performance status(PS)などを考慮する必要がある．
- 二次治療における標準的な化学療法は確立していない．
- 肺癌診療ガイドライン(2011 年 3 月)によれば，sensitive relapse では再発時の化学療法の効果が高く，re-challenge をはじめ化学療法を行うように勧められているが，refractory relapse に対する化学療法の意義は確立していない．

非小細胞肺癌に比べ，小細胞肺癌に有効な薬剤の開発は停滞している．その結果，近年では小細胞肺癌における化学療法の効果の改善も乏しい．小細胞肺癌の二次治療において，標準治療は決まっていない．しかしながら，臨床試験の結果をみながら，小細胞肺癌の二次治療について考えてみたい．

再発までの期間による二次治療効果の差異

再発小細胞肺癌は初回治療に比して化学療法や放射線療法に対する感受性が不良であるが，初回治療終了後から再発までの期間が長い症例のほうが，化学療法の有効性が高いことが報告されている[1,2]．したがって，初回化学療法が奏効し，初回治療終了後から再発までの期間が長い症例(60～90 日以上)を“sensitive relapse(治療感受性の再発)”として，初回治療が奏効していない，または初回治療終了後から再発までの期間が短い症例を“refractory relapse(治療抵抗性の再発)”として治療が行われている．1984 年から 2011 年にかけて 21 の臨床研究が対象となり，sensitive relapse(再発までの期間が 90 日以上)および refractory relapse に対する系統的解析が報告された[3]．再発小細胞肺癌 1,692 例(refractory relapse 780 例/

キーワード：sensitive relapse, refractory relapse, nogitecan(NGT), amrubicin(AMR).

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Table 1. NGTによる再発小細胞肺癌に対する主な治療成績

著者	発表年	phase	投与量 (mg/m²)	化学療法感受性	症例数	奏効率 (%)	MST (月)	grade 3/4(%)	
								好中球減少	FN
Takeda et al[6]	2003	Ⅱ	1.0	sensitive	50	26.0	9.3	92	24
Inoue et al[12]	2008	Ⅱ	1.0	sensitive	19	21.0	11.7	87	3
				refractory	11	0.0	5.4		
Jotte et al[14]	2011	Ⅲ	1.5(iv)	sensitive	117	16.9	9.9	53.3	3.6
				refractory	96		5.7		

FN：発熱性好中球減少症.

sensitive relapse 912例)における奏効率，中央生存期間(MST)はそれぞれ14.8%/27.7%(p=0.0001)，5.45ヵ月/7.73ヵ月(p=0.0035)であり，sensitive relapse群で良好な治療効果と生存期間の延長が有意に示された．また，refractory relapse群はさらなる新規治療の開発が必要であるものの，一定の治療効果が得られることが確認された．

二次治療におけるレジメン選択の考え方

二次治療においてbest supportive care(BSC)との唯一の無作為化比較第Ⅲ相試験が，初回治療終了後45日以上経過して再発を認めたsensitive relapseを対象に検討が行われた[4]．主要評価項目であるMSTは経口nogitecan(NGT，欧米ではtopotecan)群(2.3 mg/m²，day 1～5)25.9週に対して，BSC群では13.9週であり，また，NGT群の奏効率は7%と低かったが，44%がstable diseaseとなったことで化学療法群であるNGTによる生存期間の延長が認められた(p= 0.01)．

比較的全身状態が保たれたsensitive relapse症例に対して，初回化学療法と同じレジメンを再投与すること(re-challenge)の有効性が報告されているが，1980年代の報告であり，その意義は確立していない(日本肺癌学会：肺癌診療ガイドライン，2011年3月)．前述の系統的解析によれば有効性が期待できる化学療法レジメンは限られていることから，sensitive relapseへのre-challengeを推奨しているが，2012年の米国臨床腫瘍学会(ASCO)では再発までの期間が90日以上であったsensitive relapse症例65例において，re-challenge群(19例)と他剤治療群(46例)(46例中21例はamrubicin(AMR)投与)とを比較検討した成績が報告された．MSTでは両群間に有意差はなく，re-challengeを試みるよりもまずはAMRのような単剤での治療が推奨される結果であった[5]．欧米と本邦では一次治療から二次治療にわたり選択される化学療法レジメンが異なる背景などがあり，re-challengeについては前向き臨床試験による再検証を要するものと考えられる．

二次治療において推奨される化学療法レジメン

複数の比較試験や第Ⅱ相試験により，etoposide(VP-16)，irinotecan(CPT-11)，AMR，NGTなどの有効性が報告されているが，二次治療における標準的な化学療法は確立していない．NGTは米国食品医薬局(FDA)に認可されている唯一の薬剤であり，また，多くの国々での二次治療における第一選択薬となっている．一方，AMRは本邦において検討が多くなされ，その有効性が認められてきたが，現在のところ本邦のみの承認である．

NGTはDNAの複製や転写などの機能に関わるトポイソメラーゼⅠ阻害薬であり，欧米での承認用量は1.5 mg/m²であるが，本邦では開発段階で重篤な有害事象を認めたため，1.0 mg/m²の5日間連日点滴静注，3週ごとでの投与が行われている．その第Ⅱ相試験では奏効率26.0%，MSTは262日と報告された(Table 1)[6]．有害事象のうちgrade 3以上の好中球数減少は84.5%であった

Table 2. AMRによる再発小細胞肺癌に対する主な治療成績

著者	発表年	phase	投与量 (mg/m²)	化学療法感受性	症例数	奏効率 (%)	MST (月)	grade 3/4(%)	
								好中球減少	FN
Kato et al[9]	2006	II	45	sensitive	24	50.0	10.4	97	35
				refractory	10	60.0	6.8		
Onoda et al[10]	2006	II	40	sensitive	44	52.0	11.6	83	5
				refractory	16	50.0	10.3		
Inoue et al[12]	2008	II	40	sensitive	17	53.0	9.9	93	14
				refractory	12	17.0	5.3		
Ettinger et al[13]	2010	II	40	refractory	75	21.0	6.0	67	12
Jotte et al[14]	2011	III	40	sensitive	225	31.0	9.2	41.2	9.3
				refractory	199		6.2		
Kaira et al[11]	2010	II	35	sensitive	10	60.0	12.0	41.4	3.4
				refractory	19	36.8	11.0		

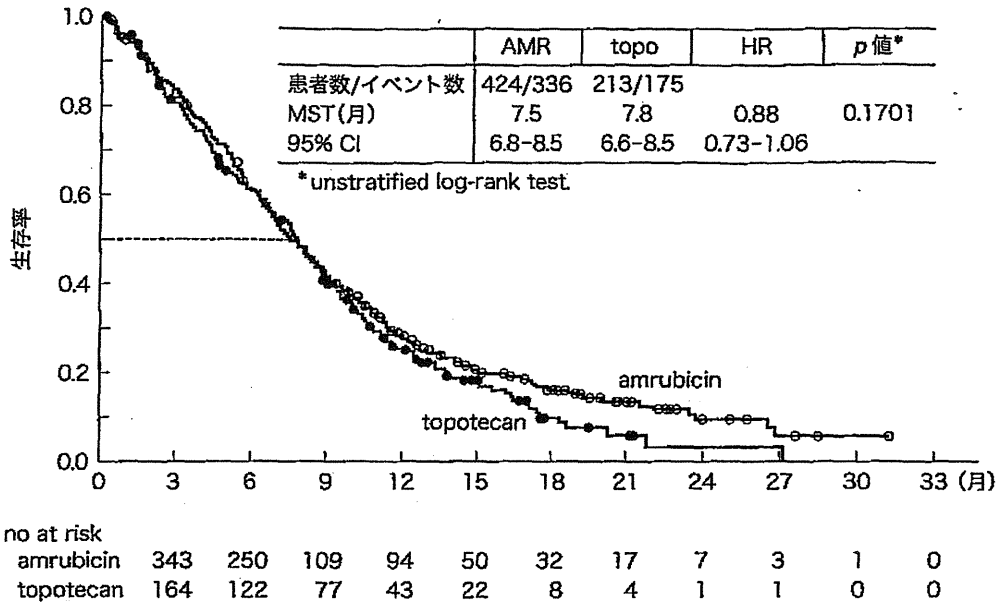
が，これらはG-CSF投与の有無にかかわらず，大部分の症例において，投与開始から14～21日間(中央値)で回復を認め，コース数を重ねることによる悪化傾向は示さなかった[7]．また，NGTは未変化体自体が活性体であり腸肝循環しないことから，CPT-11に比して重篤な下痢をきたすことは少ない(grade 3以上，1.0%)．

経口NGT 2.3 mg/m²と静注NGT 1.5 mg/m²についてのランダム化比較第III相試験では，生存をはじめ有効性，毒性や三次治療への移行率に関して有意差は認められなかった．利便性に優れることから米国では経口薬が多く用いられるようになったが，本邦では注射製剤のみの承認となっている[8]．

AMRは本邦で開発されたアントラサイクリン系のトポイソメラーゼII阻害薬であり，主な有害事象は血液毒性で，心毒性をきたしにくいといわれている．本邦からは再発小細胞肺癌に対して用量設定が異なった4つの第II相試験が報告されている(Table 2)．AMR 45 mg/m²を投与した試験では34例(refractory relapse 10例，sensitive relapse 24例)において奏効率，MSTが，refractory relapseで60%，6.8ヵ月，sensitive relapseで50%，10.4ヵ月であった[9]．AMR 40 mg/m²を投与した試験では60例(refractory relapse 16例，sensitive relapse[60日以上]44例)において奏効率，PFS，MSTはrefractory relapseで50%，2.6ヵ月，10.3ヵ月，sensitive relapseで52%，4.2ヵ月，11.6ヵ月であった[10]．AMR 35 mg/m²による試験では29例(refractory relapse 19例，sensitive relapse[90日以上]10例)において奏効率，PFS，MSTはrefractory relapseで36.8%，4.0ヵ月，11.0ヵ月，sensitive relapseで60.0%，4.0ヵ月，12.0ヵ月であった[11]．

有害事象としてgrade 3/4の好中球減少(45 mg/m²：97% vs. 35 mg/m²：41.4%)や発熱性好中球減少(45 mg/m²：35% vs. 35 mg/m²：3.4%)は用量依存性に頻度が高く，投与量決定に際しては年齢，PSを含めた全身状態の再評価を要するものと考えられる[2]．また，AMRはrefractory relapseに対してもsensitive relapseに劣らない有効性が示唆されたが，AMR(40 mg/m²，day 1～3)とNGT(1.0 mg/m²，day 1～5)とのランダム化比較第II相試験の結果は異なるものであった[12]．

この試験には60例が登録され，59例が評価可能であった(refractory relapse 23例，sensitive



	AMR	topo	HR	p値*
患者数/イベント数	424/336	213/175		
MST(月)	7.5	7.8	0.88	0.1701
95% CI	6.8-8.5	6.6-8.5	0.73-1.06	

*unstratified log-rank test.

Fig. 1.　AMR 群と NGT 群の無作為化第III相試験(ACT-1 試験)

relapse[90 日以上]36 例)．奏効率，PFS，MST は AMR 群で 38%，3.5ヵ月，8.1ヵ月(refractory relapse：17.0%，2.6ヵ月，5.3ヵ月，sensitive relapse：53.0%，3.9ヵ月，9.9ヵ月)，NGT 群では 13%，2.2ヵ月，8.4ヵ月であった(refractory relapse：0.0%，1.5ヵ月，5.4ヵ月，sensitive relapse：21.0%，3.0ヵ月，11.7ヵ月)．NGT 群において三次治療として大部分に AMR が選択され，多変量解析の結果から AMR は NGT に比して生存期間延長に寄与する可能性があり，再発小細胞肺癌に対しては AMR の投与機会を逸することなく治療を行うべきであることが示唆された．

欧米では AMR の効果と安全性を評価するため，AMR(40 mg/m^2, day 1〜3)と NGT(1.5 mg/m^2, day 1〜5)を比較する無作為化第Ⅲ相試験が実施され，2011 年の ASCO において報告された[14]．637 例が登録され，AMR 群(424 例)と NGT 群(213 例)に 2：1 の割合で無作為に割り付けられた(sensitive relapse[90 日以上])．主要評価項目である MST では AMR 群 7.5ヵ月，NGT 群 7.8ヵ月であり，有意差を認めなかったが(p= 0.1701，ハザード比 0.880[0.733-1.057])(Fig. 1)，副次評価項目である奏効率は 31.1% vs. 16.9% (p= 0.0001)，PFS は 4.1ヵ月 vs. 3.5ヵ月(p= 0.0182)であり，いずれも AMR 群のほうが有意に優れていた．食欲，咳，呼吸困難といった臨床症状の改善効果に関しても，AMR 群で有意な改善が認められた．さらにサブセット解析では，refractory relapse に限れば，AMR 群での有意な改善が認められた(6.2ヵ月 vs. 5.7ヵ月，p= 0.0469，ハザード比 0.766[0.589-0.997])(Fig. 2)．以上より，AMR は NGT と同等の有用性をもつことが欧米においても確認された．

sensitive relapse の場合，re-challenge は一つの治療選択肢である．二次治療では etoposide と irinotecan 両薬剤ともに単剤での効果は不十分なため，一次治療と同様にプラチナ製剤を併用すべきであるとされる[15]．再発まで 8 週以上経過した sensitive relapse を対象に G-CSF を併用しながら cisplatin＋VP-16 と cisplatin＋CPT-11 による毎週交替投与を行う PEI 療法の第Ⅱ相試験が実施された[16]．奏効率 78%，MST 11.8ヵ月との良好な成績であり，NGT に対する PEI 療法の優越性を検証する第Ⅲ相試験が進行している．分子標的治療薬としてチロシンキナーゼ阻害薬(imatinib, gefitinib)，血管新生阻害薬(bevacizumab)，farnesyl

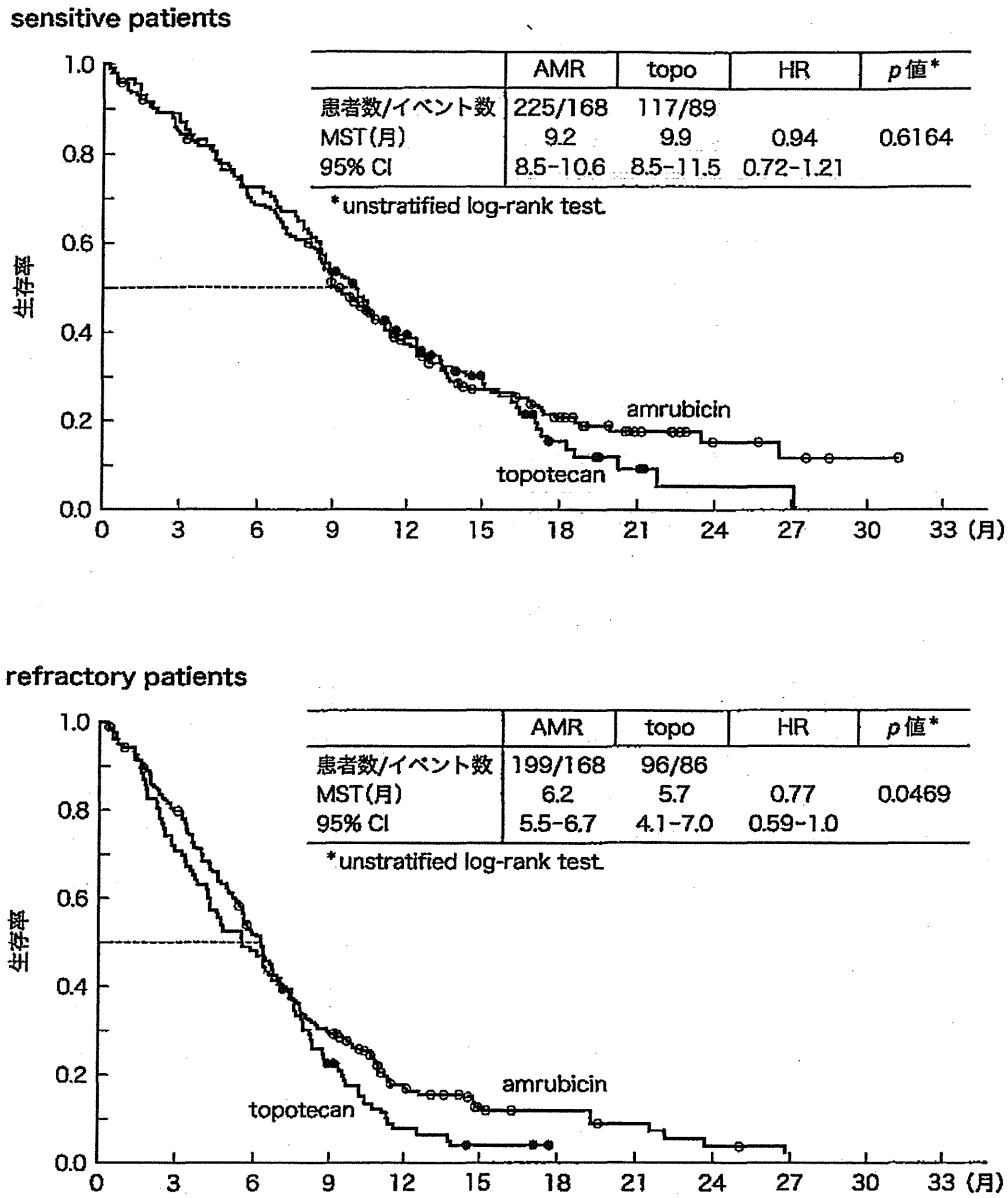


Fig. 2. AMR 群と NGT 群の無作為化第III相試験(ACT-1 試験)のサブセット解析

transferase 阻害薬などが試みられてきたが，現時点で報告されている成績は有効性に乏しい[15]．

おわりに●

初期治療導入時において sensitive に，あるいは refractory に再発するかは予測困難であり，再発時には治療抵抗性かつ進行性の経過となることから時機を逸することなく(PS 低下や oncology emergency などを避けること)，限られた治療選択肢を使い切ることが予後改善につながるものと考えられる．新規薬剤や遺伝子プロファイルに基づく治療が開発されているが，生存効果の延長が認められた治療はないのが現状である．近年，非小細胞肺癌では維持療法の有用性が示唆されており，小細胞肺癌でも同様の治療戦略の見直しが必要なのかもしれない．

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● 特 集 ● 骨転移のマネジメント

肺癌治療と骨転移マネジメント

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〔*Jpn J Cancer Chemother* 39(8): 1183-1186, *August*, 2012〕

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Summary

The preceding molecular target therapies have prolonged the life expectancy of many lung cancer patients, and some lung cancer patients have become long-term survivors. On the other hand, the proportion of patients who suffer from complications with bone metastasis and skeletal-related events (SRE) is increasing. Through management of bone metastasis, the preservation of quality of life and functional independence can be better maintained. Zoledronic acid and denosumab are usable in clinical practice; However, there are many problems in regard to treatments for bone metastasis. Lung cancer patients should be treated with bone metastasis with the coordinating cooperation between orthopedists, radiotherapists and dental surgeons. **Key words**: Lung cancer, Bone metastasis, Zoledronic acid, Denosumab, **Corresponding author**: Satoru Miura, Department of Medicine II, Niigata University Medical and Dental Hospital, 1-757 Asahimachidori, Chuo-ku, Niigata 951-8510, Japan

要旨 肺癌患者では，分子標的治療薬の導入などに伴い長期生存例も経験されるようになった。その一方で，その経過中に骨転移を合併する頻度，脊髄圧迫などの重篤なskeletal related events（SRE）を合併する頻度は増加しており，QOL維持が命題である進行期肺癌治療においてその対策は重要な課題である。近年，抗骨転移治療薬としてゾレドロン酸に加えデノスマブが臨床導入され，治療法は着実に進歩しているものの，まだまだ課題は多い。肺癌に直面する医師は，整形外科，放射線科，歯科，口腔外科との横の連携をより強め，患者のQOLを最大限維持できるように骨転移の診療に当たる必要がある。

はじめに

近年，肺癌に対する化学療法の進歩は著しく，ゲフィチニブやエルロチニブ，クリゾチニブなどの分子標的治療薬の臨床導入が進み，適切な患者と治療選択により長期生存例が多く経験されるようになった。ただし，劇的な奏効が得られるこれらの治療によっても，進行期肺癌患者で治癒を得られることはまれであり，治療の主たる目的がquality of life（QOL）の維持であることに変わりはない。肺癌患者において長期生存例が増えるにつれ，骨転移を合併する患者の頻度は増加していることが予想される。骨転移は疼痛や病的骨折，神経障害などによりQOLを障害する可能性の高い合併症であり，肺癌治療にかかわるスタッフにとってそのマネジメントを熟知することは非常に重要である。

Ⅰ．肺癌と骨転移

肺癌患者の約3人に1人が骨転移を合併するとされ，さらに骨転移で発見された癌の約1/3が肺癌であるとも報告されており，肺癌診療において骨転移のマネジメントは非常に重要な位置を占める[1,2]。肺癌の骨転移においては荷重骨である脊椎転移（42%）の頻度が最も多く，疼痛の他，病的骨折による脊髄圧迫など重篤な合併症を起こしやすいことが特徴である[3]。骨転移により起こる様々な有害事象を骨関連事象（skeletal related events: SRE）と呼び，放射線治療を要する骨病変の増悪，整形外科的手術，病的骨折，脊髄圧迫および高カルシウム（Ca）血症がSREに含まれる。わが国における進行期非

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三浦 理

小細胞肺癌（NSCLC）患者を対象とした259例のretrospectiveな検討では，全経過で30.4%（70例）に骨転移を認め，そのうち50%（35例）の患者でSREを発症している[4]。SREはQOLを著しく低下させ予後不良となることから，このSREを減少させることが骨転移治療の重要なエンドポイントとなっている。

Ⅱ．骨転移に対する治療

骨転移のうち最も頻度が多い症状として疼痛があげられ，肺癌骨転移症例の約80%に認められると報告されている[5]。疼痛緩和にはまず鎮痛薬が用いられる。癌疼痛においてはNSAIDsやオピオイドをラダーに沿って投与するが，骨転移痛は炎症を伴うためにオピオイド単剤ではなく，NSAIDsやステロイド剤などの抗炎症治療を積極的に併用することが推奨されている。さらに，最も除痛が期待できる治療は放射線治療である。約60%で疼痛緩和が可能で，約25%で完全な除痛が得られると報告されており，緩和照射として20 Gy/5 Fr，30 Gy/10 Frなどの分割照射が行われる場合が多い[6]。8 Gy/1 Frなどの単回照射も疼痛緩和効果は同等であることが示されており，期待生存期間が短い場合や連日の治療が困難な場合などに適応になる[7]。また，純β線放出核種であるストロンチウム-89（^{89}Sr）による疼痛緩和治療も限られた施設で実施可能である。^{89}SrはCa代謝が亢進した骨転移部位に選択的に集積して，腫瘍細胞，破骨細胞，造骨細胞に作用し骨転移痛の緩和をもたらす[8]。一般的な適応は標準的鎮痛薬では除痛が不十分で，外部放射線療法による治療が困難な多発性の造骨転移であるが，一過性の骨痛増強や骨髄抑制などの副作用もあるため，適応の検討は慎重に行う必要がある。

骨転移に伴う病的骨折や直接浸潤による脊髄圧迫症状は，緊急に対応が必要なSREの一つであり，肺癌診療を行う上で多く経験されるoncogenic emergencyの一つでもある。速やかに脊髄圧迫を除去するための処置として放射線療法の他に，外科的な除圧術が選択肢としてあげられる。その有効性を示す報告は少ないものの，年齢が若く不全麻痺の状況で除圧により症状の改善が期待できるなどの状況が整えば，外科的除圧術も検討されるので積極的に整形外科と連携することが肝要である[9,10]。

骨転移治療のもう一つの核をなすものとして抗骨転移治療薬があり，主にSREの抑制，骨転移痛の軽減や高Ca血症の治療薬として用いられる。骨転移の薬物療法を理解するためには，正常な骨リモデリングと骨転移に伴う骨微小環境の悪循環について知る必要がある。正常な骨形成には，血液幹細胞から分化する破骨細胞と，間葉系幹細胞から分化する骨芽細胞が重要な役割を担っている。正常な状態においては破骨細胞が骨を吸収し，骨に蓄積しているインスリン様増殖因子（insulin-like growth factor: IGF）やトランスフォーミング増殖因子-β（transforming growth factor-β: TGF-β）などの増殖因子を骨髄内に放出し，隣在する骨芽細胞の骨形成を助ける。同時に骨芽細胞は膜結合性サイトカインNF-κB活性化受容体リガンド（receptor activator of nuclear factor κB ligand: RANKL）を産生し破骨細胞への分化を促進する。これら一連の流れを骨のリモデリングと呼ぶ。この環境に癌細胞が侵入すると，IGFやTGF-βは癌細胞の増殖，生存に利用されるようになり，骨芽細胞の働きが低下する。さらに癌細胞は副甲状腺ホルモン関連蛋白（parathyroid hormone related peptide: PTHrP）やプロスタグランジンE_2（postagladin E_2: PGE_2）などの骨吸収促進性サイトカインを産生することで，骨芽細胞を刺激してRANKLの発現を誘導し，破骨細胞による骨吸収を亢進して自らが増殖，生存するためのスペースを確保する（図1）。骨転移に対する薬物療法はこれら骨微小環境内の悪循環を断ち切り，癌骨転移の進展を抑制することによりSREを減少させることが目的である。

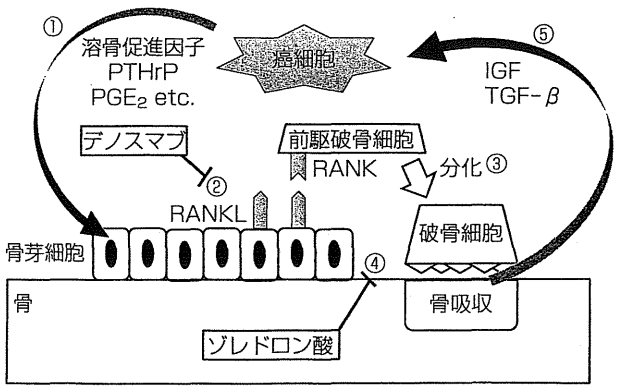

図1 癌細胞による骨微小環境の悪循環
①癌細胞はPTHrPやPGE_2といった溶骨促進因子を放出し，骨芽細胞のRANKL発現を誘導する。
②RANKLは前駆破骨細胞のRANKに結合。
③前駆破骨細胞から破骨細胞への分化を促進する。
④活性化された破骨細胞は骨吸収を促進し，癌細胞が生存するためのスペースを確保する。
⑤骨吸収により骨に蓄積されていたIGF，TGF-βなどを利用してさらに癌細胞は活性化する。
ゾレドロン酸は破骨細胞の働きを抑えて，骨吸収を抑制する。
デノスマブはRANKLの働きを抑えて，破骨細胞への分化，活性化を抑制する。

現在，骨転移治療薬はビスホスホネート（BP）と抗RANKL抗体の二つに大分される。BPはピロリン酸の類似体で強力な破骨細胞の抑制効果をもち，肺癌骨転移に対してはゾレドロン酸がわが国で唯一適応を取得し頻用されている。さらに，2012年1月に抗RANKL抗体であるデノスマブが製造承認を取得し，実地臨床に導入さ

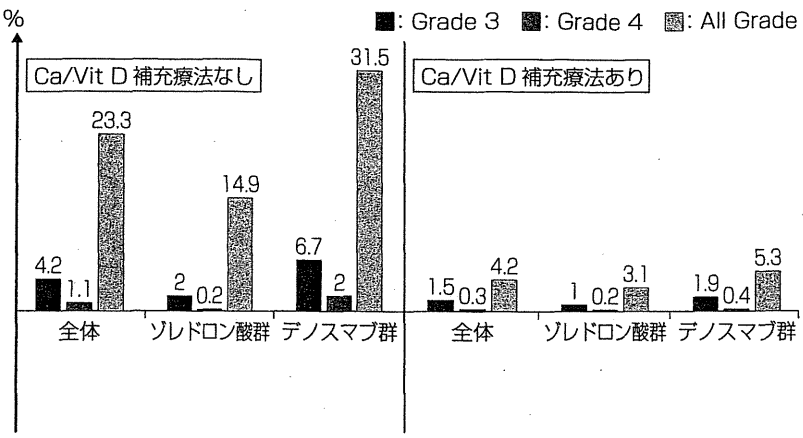

図 2

表 1[16]

	ゾレドロン酸	デノスマブ	p-value
投与方法	点滴静注 15 分 3〜4 週ごと	皮下注射 4 週ごと	
腎機能	補正が必要	補正は不要 Ccr 30 mL/min 以上投与可*	
薬価	32,354	45,155	
副作用 (all Grade)			
発熱	20.7%	15.8%	0.001
低 Ca 血症	5.8%	10.8%	NA
BRONJ**			1.0
1 年	0.6%	0.5%	
2 年	0.9%	1.1%	
3 年	1.3%	1.1%	
Grade 3〜5			
急性期反応***	14.5%	6.9%	<0.001
腎機能障害	10.9%	8.3%	0.07

*: 第Ⅲ相試験による適格規準が Ccr 30 mL/min 以上
**: Bisphosphonate related osteonecrosis of the jaw: BP 関連顎骨壊死
***: 発熱，全身倦怠感，関節痛などを含む

れた。RANKL は前述したように破骨細胞の分化，活性化に必須のサイトカインであり，癌細胞による骨微小環境変化において重要な役割を果たしている。このサイトカインの抑制による良好な SRE 抑制効果が報告されており，今後が期待されている。

Ⅲ. ゾレドロン酸とデノスマブの肺癌に対するエビデンス

ゾレドロン酸は肺癌をはじめとする固形癌の骨転移に対して，すでに有効性が確立している薬剤である。乳癌および前立腺癌を除く骨転移を有する固形癌患者 773 例 (NSCLC 378 人/50%，小細胞肺癌 58 人/8%) を対象としたゾレドロン酸とプラセボを比較する第Ⅲ相試験が報告されている[11,12]。主要評価項目である SRE 発現率はゾレドロン酸 4 mg 投与群で 38.9%，プラセボ群で 48.0% とゾレドロン酸で有意に抑制されることが示され (p=0.039)，SRE 発現までの期間を約 3 か月間有意に延長すること (236 日 vs 155 日)，SRE の発症を 36%減少させることも同時に証明されている。この試験の結果から「日本肺癌学会，肺癌診療ガイドライン 2010 年版」においてもグレード B で推奨されている[13]。さらに，上記第Ⅲ相試験のサブセット解析においては，SRE の既往がある患者に対して特にゾレドロン酸の効果が高い (SRE リスク 31%減少，p=0.009) ことが示されている[14]。また，骨代謝マーカーである尿中Ⅰ型コラーゲン架橋 N-テロペプチド (N-terminal crosslinking telopeptide of type Ⅰ collagen: NTX) が高値 (64 nmol/mmol Cr 以上) の患者は，低値の患者と比較して SRE のリスクが高い傾向にあり (RR: 1.64，p=0.068)，同時に死亡リスクが有意に高い (RR: 2.39，p=0.001) ことが報告されている[15]。この高リスク群に対して BP を投与することにより，有意に生存期間を改善することが示唆されている (RR: 0.65，

95% CI: 0.45-0.95, p=0.025)。これらはあくまでもretrospectiveなサブセット解析であるが，これらSREの高リスク群に対してはゾレドロン酸投与を積極的に行うことが推奨される。

デノスマブはRANKLに特異的に結合する完全ヒト型モノクローナル抗体であり，2012年に承認された新規の抗骨転移治療薬である。乳癌および前立腺癌以外の固形癌骨転移患者，または多発性骨髄腫患者1,776例を対象としたゾレドロン酸4mg，3週ごとと，デノスマブ120mg，4週ごとの無作為比較第Ⅲ相試験が報告されている[16]。NSCLC患者702例（39.5%）を含む対象患者において，主要評価項目である初回SRE発現までの期間にて，ゾレドロン酸との非劣性が証明された（20.6か月vs 16.3か月，HR: 0.84, 95% CI: 0.71-0.98, 非劣性p=0.0007, 優越性p=0.06)。その他全生存期間などにおいて両薬剤の差はなく，この結果をもってデノスマブは実地臨床に導入されることとなった。

ゾレドロン酸，デノスマブの特徴を表1にまとめた。投与方法，腎機能による補正の有無，薬価，副作用頻度などが両薬剤の違いとしてあげられ，これらを基に今後使い分けをしていくことになる。副作用の面でみると，発熱などの急性期反応や腎機能障害の頻度がデノスマブで低い傾向にある一方で，低Ca血症の頻度が有意に多いことが報告されている。低Ca血症の予防としてCa製剤とビタミン（Vit）D製剤の内服が海外のガイドラインでは推奨されており，予防内服により低Ca血症の頻度を減少できることがわかっている（図2)。しかし，低Ca血症は臨床的に問題となることは少なく，Ca製剤とVit D製剤の適切な補充量などの検討がほとんどなされていないことなどから，全例をルーチンに投与すべきかはまだ検討の余地がある。また，抗骨転移治療薬で問題とされる副作用として顎骨壊死（osteonecrosis of the jaw: ONJ）がある。長期間BPを使用した症例で，侵襲的歯科治療を受けた患者において発症しやすいとされる病態であるが，その詳細についてはまだ不明な部分が多く，適切な予防法，治療法も確立していない。第Ⅲ相試験の結果からはデノスマブでも少なくとも同等の頻度で発症することが予想されるため，従来と同様に口腔内環境を整えたり，歯科医との連携を行ったりすることで対応していくことが重要である。

おわりに

肺癌患者では，その経過中に骨転移を発症する頻度や脊髄圧迫などの重篤なSREを合併する頻度が多く，その対策は肺癌を治療するスタッフにとって重要な問題である。骨転移に対してはゾレドロン酸やデノスマブなどの抗骨転移治療薬を効果的に用いると同時に，整形外科，放射線治療科，歯科，口腔外科と積極的に連携しながら治療に当たる必要がある。

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