Annals of Oncology 23: 1537–1541, 2012
doi:10.1093/annonc/mdr487
Published online 29 October 2011

Postprogression survival for first-line chemotherapy of patients with advanced non-small-cell lung cancer

H. Hayashi[1], I. Okamoto[1]*, S. Morita[2], M. Taguri[2] & K. Nakagawa[1]

[1]*Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka-Sayama;* [2]*Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan*

Received 12 July 2011; revised 5 September 2011 & revised 13 September 2011; accepted 14 September 2011

Background: Given the growing number of drugs available for non-small-cell lung cancer (NSCLC), an effect of first-line chemotherapy on overall survival (OS) might be confounded by subsequent therapies. We examined the relation between postprogression survival (PPS) and OS in phase III trials of first-line chemotherapy for advanced NSCLC.
Patients and methods: A literature search identified 69 trials that were published during the past decade. We partitioned OS into progression-free survival (PFS) and PPS and evaluated the relation between OS and either PFS or PPS. We also examined whether any association might be affected by the year of completion of trial enrollment.
Results: The average PPS was longer in recent trials than in older trials (6.5 versus 4.4 months, $P < 0.0001$). For all trials, PPS was strongly associated with OS ($r = 0.82$), whereas PFS was moderately associated with OS ($r = 0.43$). The correlation between OS and PPS in recent trials was stronger than that in older trials ($r = 0.89$ and 0.66).
Conclusions: Our findings indicate that, especially for recent trials, PPS is highly associated with OS in first-line chemotherapy for advanced NSCLC, whereas PFS is only moderately associated with OS.
Key words: chemotherapy, non-small-cell lung cancer, overall survival, phase III trial, progression-free survival

introduction

Lung cancer remains the leading cause of cancer death worldwide [1, 2], with non-small-cell lung cancer (NSCLC) accounting for ~85% of lung cancer cases. Most individuals with NSCLC have metastatic disease at the time of diagnosis and therefore have a poor prognosis. The standard treatment of advanced NSCLC over the past decade has been platinum-based chemotherapy because of the moderate improvement in survival it confers [3–6]. Although many patients initially achieve clinical remission or disease stabilization with first-line chemotherapy, nearly all subsequently experience disease progression and eventually die of advanced NSCLC.

Overall survival (OS) has been traditionally recognized as the most important therapeutic objective for NSCLC patients. However, in view of the growing number of drugs and combinations thereof that are available for the treatment of such patients, any effect of first-line chemotherapy on OS might be confounded by subsequent therapies [7]. Indeed, an improvement in progression-free survival (PFS) has not necessarily resulted in an improved OS in recent randomized trials in patients with NSCLC [8, 9].

The effect of therapies instituted after disease progression on survival in clinical trials is thus of interest. However, little is known about postprogression survival (PPS) in NSCLC. In the present study, we partitioned OS of phase III trials for chemotherapy-naive patients with NSCLC into PFS and PPS and assessed the association of each with OS.

*Correspondence to: Dr I. Okamoto, Department of Medical Oncology, Kinki University Faculty of Medicine, 377-2 Ohno-higashi, Osaka-Sayama, Osaka 589-8511, Japan. Tel: +81-72-366-0221; Fax: +81-72-360-5000; E-mail: chi-okamoto@dotd.med.kindai.ac.jp

methods

search strategy and selection of trials

An independent review of PubMed citations from 1 January 2000 to 31 October 2010 was carried out. Key words included in the search were 'non-small cell lung cancer', 'clinical trial', 'advanced', and 'chemotherapy'. The search was limited to randomized controlled phase III trials and articles published in English. We reviewed each publication, and phase III studies that compared two or more first-line systemic chemotherapies (including treatment with molecularly targeted agents) for advanced or metastatic NSCLC were selected. To find any additional trials, we searched the reference lists of included trials as well as of large systematic reviews. We also checked articles that were in press at leading journals and searched websites listing abstracts from conferences (organized by the American Society of Clinical Oncology or the Federation of European Cancer Societies). We included trials that provided data for both OS and either PFS or time to progression (TTP), whether or not these parameters were explicitly defined. Trials were excluded if they investigated only immunotherapy regimens or hormonal therapies. Trials that were designed to assess combined modality treatments, including radiation therapy and surgery, were also excluded. To avoid bias, two observers (HH and IO) independently abstracted the data from the trials.

data abstraction

We analyzed in detail the primary and secondary efficacy end points, following the definitions of the authors of each trial. When not specifically

stated by the authors, we considered the primary end point to be that used for calculation of sample size. For the sake of simplicity, two end points (PFS and TTP) based on tumor assessment are collectively referred to as PFS in the present study, similar to the approach adopted in a recent report [10]. Median OS and median PFS were extracted from all trials that provided data for each treatment group. Median PPS was defined as median OS minus median PFS for each trial. We also obtained the following information from each report: year of completion of trial enrollment, number of patients randomized, number of patients in each treatment arm, number of treatment arms in each trial, proportion of patients who were male or had adenocarcinoma, and median age of the patients.

data analysis

We summarized the survival data (median OS, median PFS, median PPS, and median PFS/median OS) as the average and standard error (SE) for trial arms. SE was calculated on the basis of previously described models [11]. We also calculated the percentage of OS accounted for by PPS for each trial arm as: 100 − (100 × median PFS/median OS). To assess the relation between median OS and either median PFS or median PPS, we used Spearman's rank correlation coefficient. To account for differences in sample size among trial arms, we weighted all analyses by the number of patients in each arm. In addition, all trials were divided into two groups on the basis of the year in which trial enrollment was completed. Given that the median year for completion of enrollment in the 69 analyzed trials was 2002, we dichotomized at year 2002 (older trials, up to and including 2002; recent trials, 2003 and later) in order to evaluate a possible change in PPS, and we assessed whether the evaluated relations might be dependent on the year of completion of trial enrollment. We examined differences in the survival data between older and recent trials by normal approximation of the average survival data (z test). All reported P-values correspond to two-sided tests, and those of P-values <0.05 were considered statistically significant. Analyses were carried out with SAS for Windows release 9.2 (SAS Institute, Cary, NC).

results

characteristics of the trials

Our search yielded a total of 467 potentially relevant publications. Initially, 366 studies were excluded for at least one of the following reasons: they examined other malignancies or combined modality treatments, they were not randomized, they were phase I or II trials, they were review articles, they represented subgroup analyses, or they were duplicates. The selection process for the randomized controlled trials is shown in Figure 1. Review of the remaining 101 publications yielded 69 trials that were considered to be highly relevant for the present study. The main characteristics of the 69 phase III trials included in the analysis are listed in Table 1. A total of 37 986 patients with advanced NSCLC were enrolled, with a median number of patients per study of 433 (range 153–1725). Most of the trials had a high proportion of male patients and of patients with adenocarcinoma. The average median age of the patients was 62.3 years. Ten trials used an end point based on tumor assessment (PFS or TTP) as the primary end point, whereas OS was assessed as the primary end point in 53 trials. The other six trials used response rate or quality of life as the primary end point.

median OS, PFS, and PPS in all trials and in subgroups based on year of completion of trial enrollment

The survival data for trial arms according to the year in which trial enrollment was completed are shown in Table 2. Although the average median PFS in older (up to and including 2002) trials was the same (4.9 months) as that in recent (2003 and later) trials, the average median PPS was ~50% longer in the

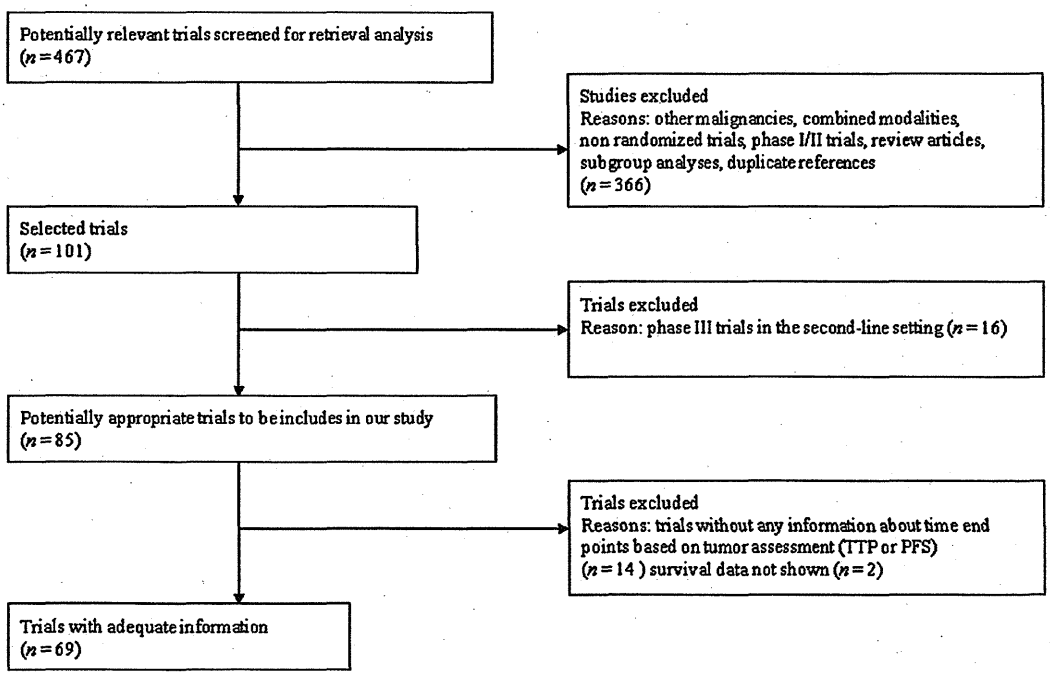


Figure 1. Flow chart showing the progress of trials through the selection process.

recent trials than in the older trials (6.5 and 4.4 months, respectively, $P < 0.0001$). The average proportion of median OS accounted for by median PPS significantly increased from 45.9% in older trials to 54.9% in recent trials ($P < 0.0001$).

relation between OS and either PFS or PPS

The relation between median OS and either median PFS or median PPS for the 151 treatment arms of the 69 trials is shown in Figures 2 and 3, respectively. We found that median PPS was strongly associated with median OS ($r = 0.82$, $P < 0.0001$) on the basis of Spearman's correlation coefficient, whereas median PFS was more moderately correlated with median OS ($r = 0.43$, $P < 0.0001$). The association between median OS and median PPS in recent trials ($r = 0.89$, $P < 0.0001$) was stronger than that in older trials ($r = 0.66$, $P < 0.0001$), whereas the correlation between median OS and median PFS in recent trials ($r = 0.55$, $P < 0.0001$) was similar to that in older trials ($r = 0.44$, $P < 0.0001$).

Table 1. Characteristics of the 69 phase III trials for advanced non-small-cell lung cancer included in the present analysis

Trial characteristic	
Median no. of patients per trial (range)	433 (153–1725)
Percentage of male patients (median)[a]	70.2
Percentage of adenocarcinoma patients[b]	51.2
Average of median age (years)[c]	62.3
Primary end point (no. of trials)	
OS	53
PFS or TTP	10
Response rate	3
Quality of life or toxicity	3
End point based on tumor assessment	
TTP	39
PFS	30
No. of treatment arms	
2	58
3	9
4	2

[a]One trial was excluded (data were not shown).
[b]Five trials were excluded (data were not shown).
[c]One trial was excluded (data were not shown).
OS, overall survival; PFS, progression-free survival; TTP, time to progression.

discussion

In the present study, we defined median PPS as median OS minus median PFS for each treatment arm of phase III trials for chemotherapy-naive patients with advanced NSCLC, as previously described [10, 12]. We also investigated the relation between median OS and either median PPS or median PFS by correlation analysis and found that median OS was more strongly associated with median PPS than with median PFS. Moreover, we also found that the correlation between median PPS and median OS was more pronounced in recent trials than in older trials and that median PPS was longer in recent trials than in older trials. This recent prolongation of PPS is likely the result of the increasing number of active compounds, such as docetaxel, pemetrexed, and epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs), which are available for second- or third-line chemotherapy in advanced NSCLC. One trial from a decade ago, when pemetrexed and EGFR-TKIs were not available, reported that only ~20% of patients received second-line chemotherapy [13]. In contrast, in the AVAiL trial, a recent large phase III trial that investigated the efficacy of cisplatin–gemcitabine with or without bevacizumab, second-line chemotherapy was administered in >60% of patients [8, 9]. Clinical trials of chemotherapy for patients with refractory NSCLC yielded a median OS of 5–8 months [14–17], which is similar to the median PPS for recent trials in our analysis. The recent widespread use of active second- and third-line therapies thus appears to have contributed to a prolongation of PPS in patients with advanced NSCLC.

Broglio and Berry [12] recently focused on PPS, which they termed survival postprogression (SPP) and defined as OS minus PFS, in a hypothetical clinical trial setting under the assumption that there was a treatment difference in PFS but not in PPS [12]. As the median PPS increased, the probability of detecting a statistically significant difference in OS decreased substantially. Even for a trial with an observed P value for improvement in PFS of 0.001, whereas there was a >90% probability for statistical significance of the difference in OS if the median PPS was 2 months, this probability decreased to only ~50% if the median PPS was 6 months. In the present study, we found that median PPS constituted more than half of median OS and that median PPS was >6 months in recent trials for NSCLC.

Table 2. Average median PFS, OS, and PPS as well as the average proportion of OS accounted for by PPS for trial arms in all trials or in trials according to year of completion of trial enrollment

Trials	No. of arms	No. of patients	Average median (months)			Average PPS/OS (%)
			PFS	OS	PPS	
All	151	37 986	4.9 (0.09)	10.3 (0.24)	5.4 (0.22)	50.1 (1.00)
Recent (2003 and later)	69	19 334	4.9 (0.13)	11.3 (0.42)	6.5 (0.37)	54.9 (1.31)
Older (up to and including 2002)	82	18 652	4.9 (0.13)	9.4[a] (0.17)	4.4[a] (0.16)	45.9[a] (1.33)

Values in brackets are standard errors.
[a]$P < 0.0001$ versus the corresponding value for recent trials (z test).
OS, overall survival; PFS, progression-free survival; PPS, postprogression survival; TTP, time to progression.

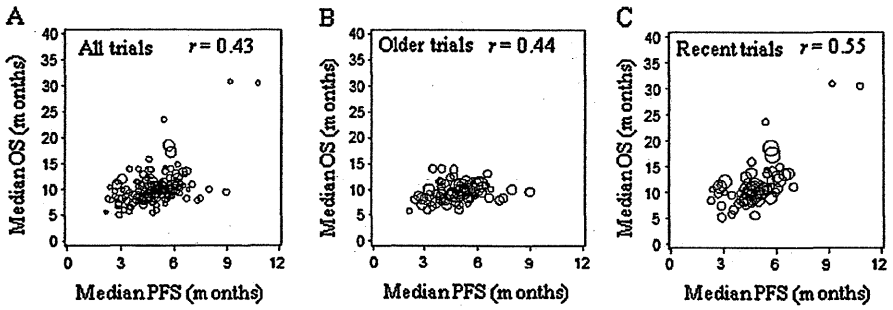


Figure 2. Relation between median overall survival (OS) and median progression-free survival (PFS) for 151 arms of 69 phase III trials for advanced non-small-cell lung cancer. (A) All trials. (B) Older trials (trial enrollment finished between 1996 and 2002). (C) Recent trials (trial enrollment finished between 2003 and 2006). The area of each circle is proportional to the number of patients in each trial arm. The *r* values represent Spearman's rank correlation coefficient.

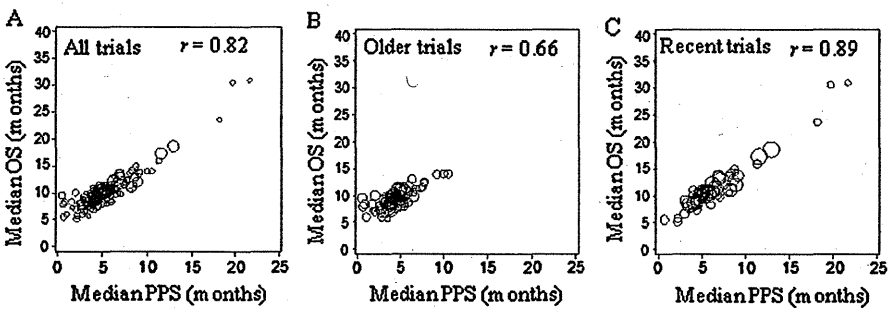


Figure 3. Relation between median overall survival (OS) and median progression-free survival (PPS) for 151 arms of 69 phase III trials for advanced non-small-cell lung cancer. (A) All trials. (B) Older trials (trial enrollment finished between 1996 and 2002). (C) Recent trials (trial enrollment finished between 2003 and 2006). The area of each circle is proportional to the number of patients in each trial arm. The *r* values represent Spearman's rank correlation coefficient.

Surrogacy of PFS for OS has often been assessed by quantifying the strength of the association between these end points at the individual level (referred to as individual-level surrogacy) and of that between the effects of treatment on these end points (trial-level surrogacy) [18–21]. Our examination of the correlation between PFS and OS was not an exercise in surrogate validation because of the lack of investigation into the correlation between the effects of chemotherapy on these end points. However, the present study has yielded the key finding that PPS, not PFS, is highly associated with OS.

The present study has several limitations. First, our analysis was based on abstracted data. The use of individual patient data might be expected to allow a better characterization of the relation between OS and other end points based on tumor assessment, including PFS and TTP. However, such an approach would restrict the analysis to a small number of trials and would hinder its replication by independent researchers. Second, the results of our study potentially have several confounders due to selection of many heterogeneous trials for analysis. The results are generally unaccountable without appropriate adjustment for patient characteristics dependent on differences in predefined eligibility criteria for enrollment in the clinical trials. Third, the assessment of disease progression is potentially subject to measurement error and bias in individual patients, and the quality of measurement for end points based on tumor assessment can vary between centers and trials. Finally, two end points (PFS and TTP) based on tumor assessment are considered as the same parameter, following the example of a previous report for advanced breast cancer [10]. PFS is defined as the time from randomization to tumor progression or death, whereas TTP is defined similarly but considers death as a time point when censoring occurs. TTP is the same as PFS if death does not occur during treatment. Given that death rarely occurs before disease progression in advanced NSCLC, we reasonably considered PFS to be the same as TTP for our analysis. Indeed, we separately analyzed clinical trials providing PFS (n = 63 arms) or TTP (n = 88 arms), and we found a consistent association between OS and PPS (data not shown). These data thus support our approach in which these two end points (PFS and TTP) are collectively referred to as PFS in the present analysis.

As far as we are aware, our study is the first to analyze PPS in advanced NSCLC. Our findings indicate that, especially for recent trials, PPS is highly associated with OS for first-line chemotherapy in patients with advanced NSCLC, whereas PFS is only moderately associated with OS. Therefore, OS remains an appropriate end point of clinical trials for chemotherapy-naive patients with advanced NSCLC. Given the great effect of PPS on OS, we propose a precise assessment of clinical course after disease progression in each clinical trial.

funding

The study was not supported by a sponsor or funding agency.

disclosure

The authors declare no conflicts of interest.

references

1. Breathnach OS, Freidlin B, Conley B et al. Twenty-two years of phase III trials for patients with advanced non-small-cell lung cancer: sobering results. J Clin Oncol 2001; 19: 1734–1742.
2. Carney DN. Lung cancer—time to move on from chemotherapy. N Engl J Med 2002; 346: 126–128.
3. Hotta K, Matsuo K. Long-standing debate on cisplatin- versus carboplatin-based chemotherapy in the treatment of advanced non-small cell lung cancer. J Thorac Oncol 2007; 2: 96.
4. Hotta K, Matsuo K, Ueoka H et al. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. J Clin Oncol 2004; 22: 3852–3859.
5. Azzoli CG, Baker S Jr, Temin S et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2009; 27: 6251–6266.
6. Wakelee HA, Bernardo P, Johnson DH, Schiller JH. Changes in the natural history of nonsmall cell lung cancer (NSCLC)—comparison of outcomes and characteristics in patients with advanced NSCLC entered in Eastern Cooperative Oncology Group trials before and after 1990. Cancer 2006; 106: 2208–2217.
7. Soria JC, Massard C, Le Chevalier T. Should progression-free survival be the primary measure of efficacy for advanced NSCLC therapy? Ann Oncol 2010; 21: 2324–2332.
8. Reck M, von Pawel J, Zatloukal P et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010; 21: 1804–1809.
9. Reck M, von Pawel J, Zatloukal P et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009; 27: 1227–1234.
10. Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. J Clin Oncol 2010; 28: 1958–1962.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–188.
12. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 2009; 101: 1642–1649.
13. Sandler AB, Nemunaitis J, Denham C et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2000; 18: 122–130.
14. Fossella FV, DeVore R, Kerr RN et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18: 2354–2362.
15. Hanna N, Shepherd FA, Fossella FV et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22: 1589–1597.
16. Kim ES, Hirsh V, Mok T et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008; 372: 1809–1818.
17. Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353: 123–132.
18. Buyse M, Squifflet P, Laporte S et al. Prediction of survival benefits from progression-free survival in patients with advanced non small cell lung cancer: evidence from a pooled analysis of 2,838 patients randomized in 7 trials. J Clin Oncol 2008; 26 (Suppl): (Abstr 8019).
19. Mauguen A, Michiels S, Burdett S et al. Evaluation of progression-free survival as a surrogate endpoint for overall survival when evaluating the effect of chemotherapy and radiotherapy in locally advanced lung cancer using data from four individual patient data meta-analyses. J Thorac Oncol 2011; 6 (Suppl 2): S464–S465.
20. Hotta K, Fujiwara Y, Matsuo K et al. Time to progression as a surrogate marker for overall survival in patients with advanced non-small cell lung cancer. J Thorac Oncol 2009; 4: 311–317.
21. Johnson KR, Ringland C, Stokes BJ et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol 2006; 7: 741–746.

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

Akihiko Gemma

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.

A. Gemma (✉)
Division of Pulmonary Medicine and Oncology,
Department of Internal Medicine, Graduate School
of Medicine, Nippon Medical School,
1-1-5 Sendagi, Bunkyo-ku,
Tokyo 113-8603, Japan
e-mail: agemma@nms.ac.jp

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

Yoshinobu Saito · Akihiko Gemma

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

Y. Saito (✉) · A. Gemma
Department of Pulmonary Medicine and Oncology,
Graduate School of Medicine, Nippon Medical School,
1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan
e-mail: yo-saito@nms.ac.jp

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

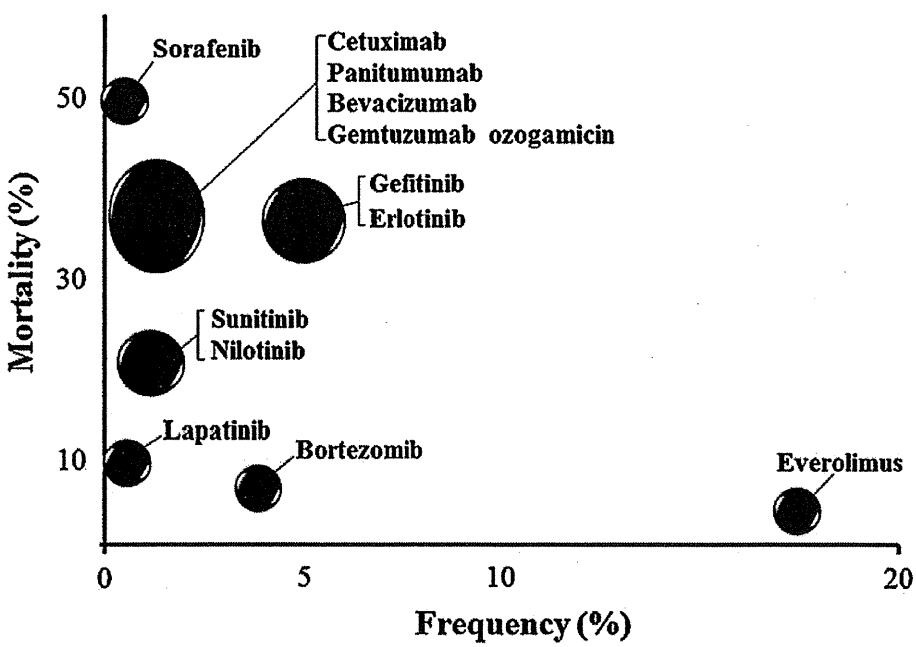


Fig. 1 A diagram showing the relationship between the frequency and the prognosis of drug-induced interstitial lung disease (DILD). The *horizontal axis* and the *vertical axis* show the frequency of interstitial lung disease (ILD) and the mortality rate from ILD, respectively. The data are based on 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.

References

1. Inoue A, Saijo Y, Maemondo M et al (2003) Severe acute interstitial pneumonia and gefitinib. Lancet 361:137–139
2. Pharmaceuticals and Medical Devices Agency (2004), Reports on Iressa Tablets 250 prospective study (special investigation). In: Pharmaceuticals and Medical Devices Safety Information. No. 206 October 2004. http://www.pmda.go.jp/english/service/pdf/precautions/PMDSI-206.pdf. Accessed Oct 2012
3. Kudoh S, Kato H, Nishiwaki Y et al (2008) Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. Am J Respir Crit Care Med 177:1348–1357
4. Kubota K, Nishiwaki Y, Tamura T et al (2008) Efficacy and safety of erlotinib monotherapy for Japanese patients with advanced non-small cell lung cancer: a phase II study. J Thorac Oncol 3:1439–1445
5. Nakagawa K, Kudoh S, Ohe Y et al (2012) Postmarketing surveillance study of erlotinib in Japanese patients with non-small-cell lung cancer (NSCLC): an interim analysis of 3488 patients (POLARSTAR). J Thorac Oncol 7:1296–1303
6. Okamoto I, Fujii K, Matsumoto M et al (2003) Diffuse alveolar damage after ZD1839 therapy in a patient with non-small cell lung cancer. Lung Cancer 40:339–342
7. Camus P, Kudoh S, Ebina M (2004) Interstitial lung disease associated with drug therapy. Br J Cancer 91(suppl 2):S18–S23
8. Makris D, Scherpereel A, Copin MC et al (2007) Fatal interstitial lung disease associated with oral erlotinib therapy for lung cancer. BMC Cancer 7:150
9. Lind JS, Smit EF, Grünberg K et al (2008) Fatal interstitial lung disease after erlotinib for non-small cell lung cancer. J Thorac Oncol 3:1050–1053
10. Okusaka T, Furuse J, Funakoshi A et al (2011) Phase II study of erlotinib plus gemcitabine in Japanese patients with unresectable pancreatic cancer. Cancer Sci 102:425–431
11. Ishiguro M, Watanabe T, Yamaguchi K et al (2012) A Japanese post-marketing surveillance of cetuximab (Erbitux®) in patients with metastatic colorectal cancer. Jpn J Clin Oncol 42:287–294
12. Takeda Pharmaceutical Company Limited (2012) http://www.vectibix-takeda.com/files/chousa.pdf (in Japanese). Accessed Oct 2012
13. Chugai Pharmaceutical Co., Ltd. (2012) http://chugai-pharm.jp/hc/ss/pr/safe/report/ava/index.html (in Japanese). Accessed Oct 2012
14. Miyakoshi S, Kami M, Yuji K et al (2006) Severe pulmonary complications in Japanese patients after bortezomib treatment for refractory multiple myeloma. Blood 107:3492–3494
15. Gotoh A, Ohyashiki K, Oshimi K et al (2006) Lung injury associated with bortezomib therapy in relapsed/refractory multiple myeloma in Japan: a questionnaire-based report from the "lung injury by bortezomib" joint committee of the Japanese Society of Hematology and the Japanese Society of Clinical Hematology. Int J Hematol 84:406–412
16. Mukai H, Ohyashiki K, Katoh T et al (2011) Lung injury associated with bortezomib therapy in Japan. Rinsho Ketsueki 52:1859–1869 (in Japanese)
17. Horiuchi-Yamamoto Y, Gemma A, Taniguchi H et al (2012) Drug-induced lung injury associated with sorafenib: analysis of all-patient post-marketing surveillance in Japan. Int J Clin Oncol. doi:10.1007/s10147-012-0438-0 (Epub ahead of print)
18. Pfizer Japan Inc. (2012) http://pfizerpro.jp/cs/sv/sutent/pms/report.html (in Japanese). Accessed Oct 2012
19. Bristol-Myers K.K. (2012) http://www.sprycel.jp/pdf/investigation/tyukankaiseki_20101006.pdf (in Japanese). Accessed Oct 2012
20. Novartis Pharma K.K. (2012) http://product.novartis.co.jp/tas/ts/pms_chukan-1.pdf (in Japanese). Accessed Oct 2012

21. Ohnishi K, Sakai F, Kudoh S et al (2006) Twenty-seven cases of drug-induced interstitial lung disease associated with imatinib mesylate. Leukemia 20:1162–1164
22. Pfizer Japan Inc. (2012) https://pfizerpro.jp/download.php?key=4yTxchfb450= (in Japanese). Accessed Oct 2012
23. Glaxo Smith Kline K.K. http://tykerb.jp/pdf/chosagaiyo.pdf (in Japanese). Accessed Oct 2012
24. White DA, Camus P, Endo M et al (2010) Noninfectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. Am J Respir Crit Care Med 182:396–403
25. Yao JC, Shah MH, Ito T et al (2011) Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 364:514–523
26. Bellmunt J, Szczylik C, Feingold J et al (2008) Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. Ann Oncol 19:1387–1392
27. Maroto JP, Hudes G, Dutcher JP et al (2011) Drug-related pneumonitis in patients with advanced renal cell carcinoma treated with temsirolimus. J Clin Oncol 29:1750–1756
28. Camus P (2003) Drug induced infiltrative lung diseases. In: Schwarz MI, King TE (eds) Interstitial lung disease, 4th edn. Decker, London, pp 485–534
29. Müller NL, White DA, Jiang H et al (2004) Diagnosis and management of drug-associated interstitial lung disease. Br J Cancer Suppl 2:S24–S30
30. Novartis Pharma K.K. (2012) http://product.novartis.co.jp/afi/tg/te_afi_RCC_201209.pdf (in Japanese). Accessed Oct 2012
31. Pfizer Japan Inc. (2012) http://pfizerpro.jp/documents/info/tor01info.pdf (in Japanese). Accessed Oct 2012

≪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).

* A. Ishiguro：弘前大学腫瘍内科学；Y. Saijo(教授)：新潟大学医学部総合医学教育センター腫瘍学分野．

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❷

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❷

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		

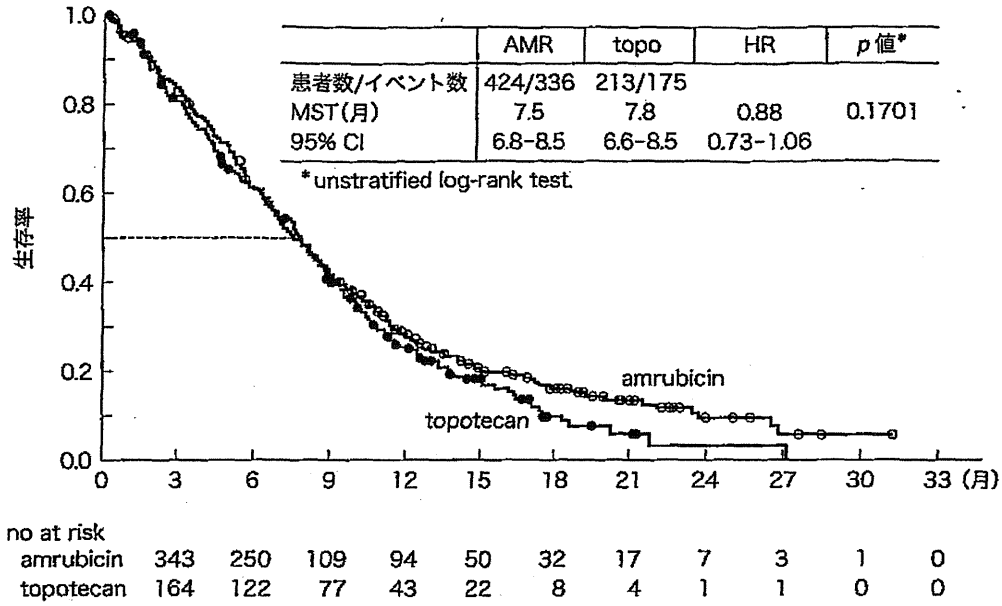
が，これらはG-CSF投与の有無にかかわらず，大部分の症例において，投与開始から14～21日間(中央値)で回復を認め，コース数を重ねることによる悪化傾向は示さなかった[7]．また，NGTは未変化体自体が活性体であり腸肝循環しないことから，CPT-11に比して重篤な下痢をきたすことは少ない(grade 3以上，1.0%)．

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.

no at risk											
amrubicin	343	250	109	94	50	32	17	7	3	1	0
topotecan	164	122	77	43	22	8	4	1	1	0	0

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

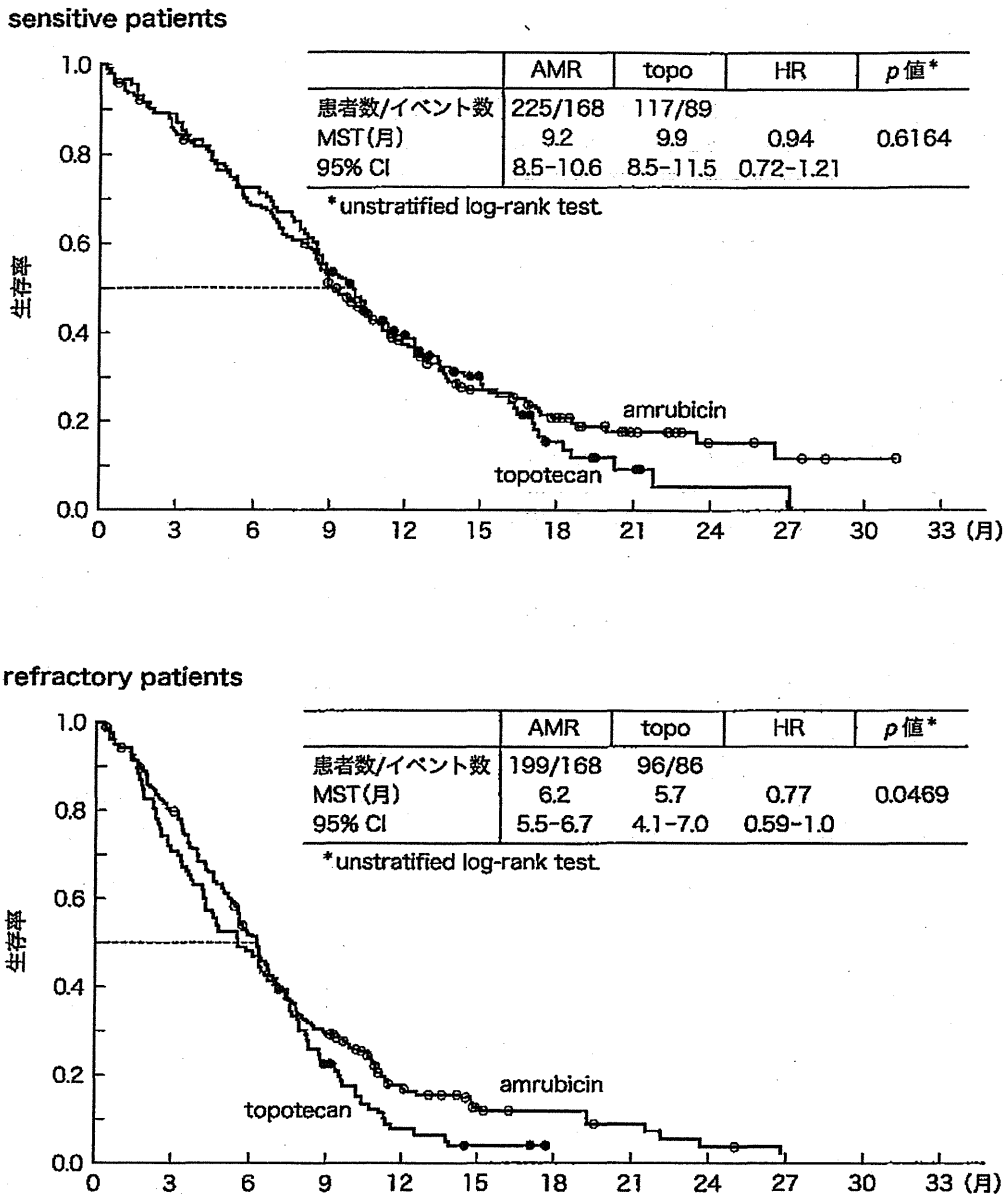


Fig. 2. AMR 群と NGT 群の無作為化第III相試験(ACT-1 試験)のサブセット解析

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．

文　献

1) Ardizzoni A et al：Topotecan, a new active drug in the second-line treatment of small-cell lung cancer：a phase II study in patients with refractory and sensitive disease：The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. J Clin Oncol 15：2090, 1997
2) Kim YH et al：Performance status and sensitivity to first-line chemotherapy are significant prognostic factors in patients with recurrent small cell lung cancer receiving second-line chemotherapy. Cancer 113：2518, 2008
3) Owonikoko TK et al：A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. J Thorac Oncol 7：866, 2012
4) O'Brien ME et al：Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 24：5441, 2006
5) Wakuda K et al：Efficacy of rechallenge chemotherapy in patients with sensitive relapsed small cell lung cancer. J Clin Oncol 30[Suppl]：abstr 7088, 2012
6) Takeda K et al：A phase II study of topotecan in patients with relapsed small-cell lung cancer. Clin Lung Cancer 4：224, 2003
7) ハイカムチン注射用 1.1 mg. 医薬品インタビューフォーム，2011年2月
8) Eckardt JR et al：Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol 25：2086, 2007
9) Kato T et al：Phase II trial of amrubicin in patients with previously treated small cell lung cancer (SCLC). J Clin Oncol 24[Suppl]：abstr 7061, 2006
10) Onoda S et al：Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer：Thoracic Oncology Research Group Study 0301. J Clin Oncol 24：5448, 2006
11) Kaira K et al：A phase II study of amrubicin, a synthetic 9-aminoanthracycline, in patients with previously treated lung cancer. Lung Cancer 69：99, 2010
12) Inoue A et al：Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer：North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol 26：5401, 2008
13) Ettinger DS et al：Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. J Clin Oncol 28：2598, 2010
14) Jotte R et al：Randomized phase III trial of amrubicin versus topotecan (Topo) as second-line treatment for small cell lung cancer (SCLC). J Clin Oncol 29 [Suppl]：abstr 7000, 2011
15) Kim YH, Mishima M：Second-line chemotherapy for small-cell lung cancer (SCLC). Cancer Treat Rev 37：143, 2011
16) Goto K et al：Multi-institutional phase II trial of irinotecan, cisplatin, and etoposide for sensitive relapsed small-cell lung cancer. Br J Cancer 91：659, 2004