Clinical Development of Anticancer Drugs Can Be enhanced Using Efficacy Data of Small Population Clinical Trials

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Abstract

Background

Although there are accelerated approval pathways based on the data of small populations and surrogate endpoints, the concern that these pathways authorize the use of inefficacious drugs based on limited data from earlier phase clinical trials remains. We retrospectively investigated the efficacy of anticancer drugs in small and large clinical trials and verified whether small clinical trials could reflect the efficacy results of large clinical trials.

Design:

All anticancer drugs approved in Japan or whose development was terminated from 2015 to 2019 were searched. The median overall survival (OS), median progression-free survival (PFS), and overall response rates (ORR) between small clinical trials (sample size ≤ 100) and large clinical trials (sample size >100) with identical target populations and treatment settings were compared. Simple linear regression and Spearman's correlation analyses were performed.

Results

A total of 61 comparable small and large clinical trials were identified. For all endpoints, significant linear trend and correlation were detected ($P < 0.001$). In particular, the correlation coefficients of median OS and ORR were high (0.852 and 0.873, respectively).

Conclusion

The median OS, median PFS, and ORR data of small clinical trials precisely reflected the efficacy data of large clinical trials. Thus, the efficacy data of small clinical trials can be used to predict the efficacy data of a large population. These results support the accelerated approval pathway based on promising efficacy data of small populations in anticancer drug development.

1. Introduction

There are guidelines providing several pathways to expedite novel drug development and marketing authorization approval for unmet medical needs in the United States (US), Japan, and the European Union, and a waiver may be granted for conducting confirmatory clinical trials under specific conditions [1]. Many anticancer drugs have been approved based on the data of small populations and surrogate endpoints without the data of confirmatory clinical trials by following an accelerated approval pathway [2, 3]. However, whether it is appropriate to allow accelerated approval without a confirmatory clinical trial is controversial. Specifically, there is a risk that small, early phase clinical trials do not reflect the efficacy

data of large, randomized clinical trials because the small sample size in early phase clinical trials does not account for differences in patient characteristics [4]. It is believed that accelerated approval based on data of small populations and early phase clinical trials cannot assess the efficacy profile of compounds appropriately and, thus, may lead to the approval of the use of inefficacious drugs [5]. Previous reports have compared the efficacy data of phase II and phase III clinical trials to confirm whether they provided comparable results [6, 7]. However, several anticancer drugs have been approved based on limited data from earlier phase clinical trials (e.g., only phase I) with a limited sample size [8]. Thus, investigations comparing the efficacy data between only phase II and phase III clinical trials cannot completely address concerns regarding the accelerated approval of anticancer drugs. Therefore, further retrospective investigation is warranted to confirm whether small clinical trials (including phase I and phase I/II) of anticancer drugs can reflect the efficacy data of large clinical trials. This will provide insights regarding the validity of accelerated approval pathways based on the limited efficacy data of small populations and early phase clinical trials.

Although technologies are continuously progressing and many anticancer drugs have been developed, there continues to be a high unmet need of novel curative treatment options in the field of oncology [9, 10]. Currently, many phase III clinical trials are being conducted for anticancer drug development, although guidelines allow the approval of novel drugs based on surrogate endpoints without confirmatory clinical trials. However, large confirmatory clinical trials are time-consuming and costly. For example, it took approximately four years for drugs with accelerated approval to complete post-approval confirmatory clinical trials and convert their accelerated approval to regular approval [3]. Moreover, the estimated median cost of a pivotal clinical trial is \$19.0 million, and trials with a control arm are much more expensive than those without a control arm [11]. In addition to the challenges mentioned above, there is also the ethical consideration of confirmatory trials that sometimes, patients may already be aware of previous reports of investigational products being more efficacious and less toxic than the standard of care (e.g., chemotherapy) and may be enrolled in the standard of care arm of the clinical trial, despite their wishes to receive the investigational drug [12].

Between 2009 and 2013, the US Food and Drug Administration (FDA) granted accelerated approval to 22 drugs for 24 indications that required the completion of 38 post-approval confirmatory clinical trials. Half of the 38 post-approval confirmatory clinical trials have already been completed with no reported withdrawal of accelerated approval [10]. However, the question remains: can we appropriately assess the efficacy profile of drugs using small clinical trials? Because of the limited instances of the withdrawal of approved compounds in the accelerated approval scheme, we hypothesized that small clinical trials, including early phase clinical trials (e.g., phase I and I/II), may accurately reflect the efficacy of large clinical trials regardless of randomization. This investigation aimed to compare the efficacy data of small and large clinical trials and test the hypothesis above.

2. Methods

2.1 Clinical trial selection

In this investigation, the efficacy data of small and large clinical trials with comparable study design settings were extracted and compared. We constructed two databases of compounds approved as anticancer drugs and those unapproved but expected to be useful as anticancer drugs in Japan. The anticancer drugs approved in Japan from 2015 to 2019, including those with new therapeutic agent approval and those with supplemental approval (already approved for other indications, other dose levels, or other regimens), were extracted from the website of the Pharmaceuticals and Medical Devices Agency (PMDA). We defined clinical trials in which the sample size of the investigative product arm was ≤ 100 as a small clinical trial because the median sample size of the clinical trials that supported accelerated approval was approximately 100 [2, 10, 13], whereas large clinical trials had a sample size of >100 . Small and large clinical trials that enrolled a population with approved indications and met the pairing criteria below were searched in the Common Technical Document (CTD) registered on the PMDA's website and published articles.

2.2 Pairing criteria

- Enrolled identical tumor type
- Identical gene mutation or antigen expression when required for clinical trial participation
- Identical treatment line setting
- Identical dose level and regimen of investigative product
- Identical dose level and regimen of combinatory treatment in case of a combinatory clinical trial

Unapproved compounds were also within the scope of this investigation and were noted as “development failure cases.” Unapproved compounds were identified from the repository of phase III clinical trials from ClinicalTrials.gov funded by industry and enrolled cancer patients. The search terms “cancer,” status “terminated,” completion date “from 2015 to 2019,” study type “interventional,” and study phase “phase III” were searched. Pediatric phase III clinical trials were outside the scope of this study. After the identification of development failure cases, we constructed a dataset of small and large clinical trials that met the pairing criteria. We also confirmed that none of the compounds from the development failure cases had been approved in Japan.

2.3 Data collection

We analyzed the median overall survival (OS), median progression-free survival (PFS), and overall response rate (ORR), which are key efficacy endpoints in almost all clinical trials of anticancer drugs. These data of the approved anticancer drugs in Japan were extracted from the CTD registered on the PMDA's website or published articles. The data of development failure cases were extracted from the ClinicalTrials.gov repository and other published articles. The median PFS and ORR data of clinical trials utilizing different assessment criteria or different versions of the assessment criteria were excluded from the analysis. Moreover, clinical trials where the median OS and median PFS were not obtained were not included in the analysis. When there were multiple small or large clinical trials of the same compound that met the pairing criteria, all pairs were included in our analysis. For example, if two small clinical trials

and one large clinical trial met the pairing criteria, two pairs of the small clinical trials and the large clinical trial would be analyzed.

2.4 Data Analysis

Simple linear regression analysis was performed to assess the relationship between the efficacy data of small and large clinical trials, as well as the predictability of efficacy data in large clinical trials based on that of small clinical trials. Furthermore, Spearman's rank correlation analysis was performed to assess the correlation of data of each efficacy endpoint between large and small clinical trials. All statistical analyses were performed using EZR software version 1.54 with $\alpha = 0.05$ as the threshold of statistical significance [14].

3. Results

A total of 142 drugs were approved in Japan and 128 phase III clinical trials were terminated from 2015 to 2019. From these trials, 61 pairs of small and large clinical trials that met the pairing criteria were identified. Forty-seven pairs consisted of approved anticancer drugs, and fourteen pairs consisted of development failure cases. Additionally, the median OS, PFS, and ORR were obtained from 24, 26, and 49 pairs, respectively. The characteristics of the analyzed pairs are listed in Table 1. The median sample sizes of the small and large clinical trials were 36 and 240, respectively, and approximately half of the small clinical trials were phase I or I/II.

The mean and standard deviation of the median OS, median PFS, and ORR in small and large clinical trials are also shown in Table 1, and similar efficacy data were observed in small and large clinical trials. In particular, the difference in median PFS and ORR was only 0.1 months and 1.6%, respectively. Scatterplots of the median OS, median PFS, and ORR in small and large clinical trials are shown in Fig. 1.

The results of the simple linear regression analysis and Spearman's rank correlation analysis are shown in Table 2. A significant linear trend and correlation in the median OS, median PFS, and ORR between small and large clinical trials were observed.

Table 1
Characteristics of 61 pairs of small and large clinical trials

	Total N (%)	Median overall survival N (%)	Median progression-free survival N (%)	Overall response rate N (%)
Total	61	24	26	49
Approved anticancer drug	47 (77.0)	12 (50.0)	16 (61.5)	41 (83.7)
Development failure cases	14 (23.0)	12 (50.0)	10 (38.5)	8 (16.3)
Tumor type				
Hematologic malignancy	25 (41.0)	2 (8.3)	4 (15.4)	23 (46.9)
Solid malignancy	36 (59.0)	22 (91.7)	22 (84.6)	26 (53.1)
Line of treatment				
1st line	17 (27.9)	5 (20.8)	3 (11.5)	13 (26.5)
Later line	44 (72.1)	19 (79.2)	23 (88.5)	36 (73.5)
Treatment				
Monotherapy	25 (41.0)	15 (62.5)	13 (50.0)	18 (36.7)
Combinatory therapy	36 (59.0)	9 (37.5)	13 (50.0)	32 (62.3)
Median sample size (interquartile range) [range]				
Small clinical trial	36 (16.0-61.0) [6-100]	53 (35.0-64.0) [21-100]	51 (36.0-62.5) [6-100]	31 (8.0-54.0) [6-100]
Large clinical trial	240 (194.0-346.0) [109-682]	237 (184-337.8) [111-682]	220 (187.0-333.0) [109-682]	240 (195.0-351.0) [109-682]
Randomized clinical trial				
Small clinical trial	14 (23.0)	13 (54.2)	11 (42.3)	8 (16.3)
Large clinical trial	52 (85.2)	19 (79.2)	19 (73.1)	44 (89.8)
Phase				
Small clinical trial				

	Total N (%)	Median overall survival N (%)	Median progression-free survival N (%)	Overall response rate N (%)
I	15 (24.6)	2 (8.3)	2 (7.7)	14 (28.6)
I/II	15 (24.6)	3 (12.5)	8 (30.8)	13 (26.5)
II	25 (41.0)	13 (54.2)	10 (38.5)	19 (38.8)
II/III	1 (1.6)	1 (4.2)	1 (3.8)	0 (0)
III	5 (8.2)	5 (20.8)	5 (19.2)	3 (6.1)
Large clinical trial				
I	0 (0)	0 (0)	0 (0)	0 (0)
I/II	6 (9.8)	3 (12.5)	5 (19.2)	3 (6.1)
II	5 (8.2)	2 (8.3)	3 (11.5)	4 (8.2)
II/III	3 (4.9)	3 (12.5)	2 (7.7)	1 (2.0)
III	47 (77.0)	16 (66.7)	16 (61.5)	41 (83.7)
Region				
Small clinical trial				
Single region	37 (60.7)	8 (33.3)	11 (42.3)	34 (69.4)
Multiple region	23 (37.7)	15 (62.5)	14 (53.8)	14 (28.6)
Unknown	1 (1.6)	1 (4.2)	1 (3.8)	1 (2.0)
Large clinical trial				
Single region	1 (1.6)	0 (0)	0 (0)	1 (2.0)
Multiple region	60 (98.4)	24 (100)	27 (100)	48 (98.0)
Mean of each efficacy endpoint (Standard deviation) [range]				
Small clinical trial		17.3 months (9.6) [3.6-51.4]	7.7 months (6.4) [1.6-35.7]	54.0% (27.6) [0-100]
Large clinical trial		14.1 months (6.2) [3.0-32.5]	7.6 months (6.7) [1.4-35.7]	52.4% (26.1) [3.7-92.9]

Table 2

Results of linear regression analysis and correlation analysis between small and large clinical trials

	Linear regression analysis			Correlation analysis	
	Coefficient	Standard error	<i>P</i> value	Correlation coefficient	<i>P</i> value
Median overall survival	0.598	0.054	< 0.001	0.852	< 0.001
Median progression-free survival	1.000	0.062	< 0.001	0.838	< 0.001
Overall response rate	0.833	0.065	< 0.001	0.873	< 0.001

4. Discussion

In this study, the correlation of the efficacy data between small and large clinical trials was investigated to assess the reliability of the efficacy data of small clinical trials. As mentioned above, linear regression analysis indicated a significant linear trend in the median OS, median PFS, and ORR data between small and large clinical trials; correlation analysis showed that the correlation coefficients between both clinical trials were high for all endpoints, and the correlation coefficients of median OS and ORR were >0.85, the threshold used for the assessment of the validation of surrogate endpoints [15]. Thus, our results show that median OS, median PFS, and ORR data of small clinical trials properly reflect that of large clinical trials. Additionally, it is noteworthy that even when the sample size of the small clinical trial is limited (approximately 30–50), the median OS, median PFS, and ORR still accurately reflect the data from large clinical trials. This finding supports the use of the accelerated approval pathway, which is based on promising data obtained from small populations in the early phase. These data suggest that pharmaceutical companies can be confident in the efficacy data of small clinical trials and should not expect more efficacious data in future large clinical trials.

It has been reported that phase III trials of several specific compounds failed despite predecessor trials showing promising results [16, 17]. However, significant differences in the median OS, PFS, and ORR between comparable phase II and III clinical trials of anticancer drugs listed by the FDA were not observed, and their phase III trials failed to show the significant benefit of investigative products, compared with comparators [16]. In the report from Lara and Redman [17], there was a discrepancy in the concomitant medication setting, which potentially affected the efficacy data of the phase II and III clinical trials. In our investigation, we evaluated clinical trials with a more comparable study design, including the combinatory treatment setting, which potentially impacts the efficacy data based on pairing criteria. This could have caused the differing results of our investigation.

Furthermore, Vreman et al. [6] studied the efficacy data between phase II and III clinical trials of anticancer drugs and reported no consistent differences in the median OS, PFS, and ORR data, similarly

to the outcome of our investigation. However, while their investigation included only phase II and III clinical trials, our investigation included earlier phase clinical trials, including phase I and I/II. Therefore, the mean sample size of the small clinical trials in our analysis was 40.1, which was smaller than that of the investigation by Vreman et al., which reported a mean sample size of 85. Nevertheless, a correlation between small and large clinical trials was observed. Moreover, Vreman et al. reported only on compounds that were submitted to the European Medicines Agency for approval and may have therefore been biased. The efficacy data of these phase III clinical trials tended to reflect that of phase II clinical trials or produce more efficacious data. In our investigation, the efficacy data of development failure cases were included, and almost half of the samples in the median OS dataset were those of clinical trials of development failure cases. Nevertheless, a significant linear trend and strong correlation were observed in the median OS of small and large trials. Additionally, in a study by Zia et al. [7], a 12.9% higher ORR was observed in phase II than in phase III clinical trials. Meanwhile, our study demonstrated a 1.6% higher ORR in small clinical trials than in large clinical trials. One possible reason for this discrepancy is that we included only eight pairs of clinical trials of development failure cases in the ORR dataset and Zia et al. could have included more compounds whose development was terminated due to the unexpected and inefficacious results observed in phase III clinical trials, compared to those in phase II clinical trials. Another possible cause for the discrepancy is that we chose a more homogeneous patient population. Approximately 27% (13 pairs) of small and large clinical trials included in the ORR dataset enrolled cancer patients with specific antigen or gene mutation expression. Meanwhile, Zia et al. [7] searched for clinical trials investigating chemotherapeutic regimens from 1998 to 2003, and it is possible that these clinical trials investigated less specific and broader patient populations regardless of specific antigen or gene mutation expression. Therefore, it is possible that they compared the efficacy data of clinical trials that enrolled a more heterogeneous patient population with more inter-clinical trial variability and differences in patient characteristics. This could result in an efficacy gap between phase II and phase III clinical trials.

It is well-known that large clinical trials comparing the investigative product with the standard of care or placebo provide insights into the efficacy and safety of the new treatment option based on the high amount of patient data. However, development of anticancer drugs is active and fast owing to the advanced technology and quickly changing standard of care [18]. Therefore, the need for faster development of anticancer drugs has been growing, and conducting time-consuming, large, randomized phase III clinical trials is no longer ideal for anticancer drug development because it is possible that the standard of care will change before a large clinical trial can be completed, making its findings obsolete. In addition, phase III studies are costly, and a placebo-controlled clinical trial is even more expensive than studies without a control group [11, 19]. Thus, a limited research and development budget provides a challenge to the further development of health technology. As mentioned above, there is an ethical challenge regarding patient enrollment in the comparator arm of randomized, confirmatory clinical trials. In our study, more than 85% of large clinical trials were randomized and a total of 9,150 patients were enrolled in the comparator arm of a placebo-controlled or active-controlled trial. Moreover, our database included 27 large clinical trials that targeted patients who received the treatment previously and

experienced disease progression. Therefore, it is expected that a number of patients were hoping to receive new treatment and participated in the clinical trials but were enrolled in the standard of care or placebo arm of the clinical trial previously. We believe that the accelerated approval pathway can help eliminate the challenges of large clinical trials by gaining patients earlier access to novel drugs and reducing the time, cost, and ethical dilemma of confirmatory clinical trials.

Finally, we extracted the data of compounds whose clinical trials in ClinicalTrials.gov were terminated as development failure cases. However, there are also compounds in phase III clinical trials registered as “completed” whose development was stopped or paused by the pharmaceutical company due to unexpected efficacy and safety results in clinical trials. These cases were not evaluated in our datasets as development failure cases.

Conclusion

To summarize, our research showed that small clinical trials replicated the efficacy data of comparable large clinical trials and could accurately predict the efficacy results of a large population. These results support the application of the accelerated approval pathway based on the data of a small population and early phase clinical trials in anticancer drug development.

Declarations

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest:

Keiichi Sawachi is an employee of Astellas Pharma Inc.; however, employment in the company has not influenced the results and discussion presented in this paper. All remaining authors have declared no conflicts of interest.

Research involving Human Participants and/or Animals:

Not applicable. No specific investigation involving human participants and/or animals is applicable because this investigation was a pooled retrospective analysis of efficacy data in the clinical trials of anticancer drugs.

Informed consent:

Not applicable. This investigation was a pooled retrospective analysis of efficacy data in the clinical trials of anticancer drugs. Per standard requirements, no informed consent was required.

Author Contributions:

Data collection and analysis were performed by Keiichi Sawachi. Keiichi Sawachi, Naoki Matsumaru, and Katsura Tsukamoto analyzed and interpreted the data, drafted the manuscript, and approved the final manuscript.

Data Availability:

All data generated or analyzed during this investigation are included in the published articles, CTD registered on the PMDA's website, and ClinicalTrials.gov repository.

Ethics Approval:

This investigation does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate:

Not applicable. This investigation was a pooled retrospective analysis of efficacy data in the clinical trials of anticancer drugs. Per standard requirements, no informed consent was required.

Consent to publish:

Not applicable.

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Figures

Figure 1

Scatterplots of median OS, PFS, and ORR in both types of trials

OS, overall survival; PFS, progression-free survival; ORR, overall response rate