[Original Article]

A Survey on Biostatistical Consulting at Japanese Medical Institutes

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ABSTRACT

This article reports a survey on biostatistical consulting at Japanese medical institutes, which included the information on when, where and to whom statistical consulting is provided. The results of our survey bring to light the various empirically-predicted problems involved in biostatistical consulting in Japan, where the demand of biostatisticians has grown rapidly. We discuss the issues making comparisons among the results of this survey, and the surveys in the United States and Germany. (**Jpn Pharmacol Ther 2014 suppl 1 ; 42 : s33-s44**)

KEY WORDS Statistical consulting, Biostatistics, Survey

1. Introduction

The importance of statistical consulting in academic institutes has been discussed since pragmatism is fitted to be the philosophic foundation in modern science[1] and widely accepted not only for improving the quality of the research but also for its financial utility[2] or educational application.[3~5] It has been vigorously discussed on how to organize the statistical consulting unit in colleges,[6] universities,[7~9] and clinical research institutes[10,11] especially in the United States. The most of study conclusion reached is that a separately funded consulting center operated as a division of a department of statistics is the most appropriate way to provide statistical consulting, then, there exist more than 80 statistical centers or units in the United States or other research universities at the time when this paper is written in 2013 (http:/ /www.cstat.msu.edu/beyond/other_centers_other_univ.aspx).

However, few of the articles on statistical consulting report empirical data regarding what statisti-

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Table 1 Backgrounds of the biostatistical consultation units which have the open website for consultation

	Number of units	%
Country		
USA	19	70.3
Canada	3	11.1
Other	5	18.5
Institutional type		
University	14	51.9
Medical institute	7	25.9
School of Public Health	3	11.1
College	3	11.1

cal consultants actually do. One of those is an earlier work by Niland et al.[12] investigated the organizational structures, salary ranges, sources of funding, computer resources and operational concerns of biostatistical consulting units in the North America. They pointed out the issues in providing biostatistical consulting in research institutes at that time, such as inadequate institutional funding, lack of coauthorship on collaborative manuscripts or insufficiency of time for independent research as major issues. The more recent work by Gullion and Berman[13] got an overview of the activities of statistical consultants in any fields, i. e. business, education, agriculture, ecology, medicine, public health, manufacturing, engineering, and so on. It showed that consultants in clinical research had the highest percentage of PhDs and had the fewest years of experience and the statistical practice pattern is also much different from those of statisticians in other fields. Another recent work by Windman and Kauermann[14] gave a view into the practice of statistical consulting at German universities and showed that the culture of consulting is better developed in medicine than in business and economics, which is much difference in the United States. Their observations suggest it is important to consider cultural background, educational system in statistics and other backgrounds and current situations in each country when we discuss how to organize biostatistical consulting.

In order to get information on the operational structures, procedures, infrastructure and common concerns for the activities of biostatistical consulting in Japan, we conducted a survey of Japanese academic clinical research centers or hospitals taking the statistician's point of view. This paper presents a summary of the survey discussing the issues making an international comparison.

2. Methods

2.1 Population and Procedure

We found there were 15 academic clinical research centers or hospitals in Japan, in which a department, section or unit of biostatistics were founded at least three years ago with at least one statistician at a junior faculty level. This restriction was imposed because it was considered we needed at least three years to accumulate a certain amount of experience of statistical consulting at each center. We use hereinafter the word "unit" to refer to a department, section or unit of biostatistics in each clinical research centers or hospitals.

For each of the clinical research center or hospital defined above a contact person was approached by e-mail and invited to fill out an online questionnaire.

2.2 Questionnaire

The questionnaire consists of 20 questions to get an overview of who (Q8 and Q13), to whom (Q3 and Q4), and how (Q10 and Q11) statistical consulting is provided. Q1 and Q2 ask demographic information of clinical centers/hospitals. We asked which items from a list of 27 choices were often requested as the contents of a consultation (Q5). To make the list of choices for this question, we did a survey for 27 open websites of consulting units in the United States and other countries which clearly stated the subjects which area are offered for biostatistical consultation, because there was no previous report for this subject to our knowledge, while there was a report for more detail topics for biostatistical consultation in Deutsch et al.[4] Among 27 websites, 70% websites were managed by the statistical units in the United States, and 51% units were affiliated with the university (**Table 1**). Based on the result shown in **Table 2**, we chose the topics included in Q5. Respondents could specify in a text field in Q6 a response that we did not provide in Q5.

We also asked how much time is spent for statistical consulting (Q9 and Q12), fee for consultation (Q14 and Q15), general results of the first consultation (Q7) and whether statistical consulting is incorporated in the teaching program of the biostatistical section (Q16). Additionally there were open questions to answer concerns in providing biostatistical consulting at the affiliated center/hospital and items

Table 2 Subject area/topics for biostatistical consultation appeared on the websites of biostatistical consulting units in other countries

area/topics for consultation	number of units	%
data analysis/statistical analysis of data	22	81.5
designing study/study design	20	74.1
sample size/power analysis	20	74.1
results interpretation	11	40.7
database management/cleaning	10	37.0
grant application/proposal	9	33.3
report/publication writing/manuscript preparation	9	33.3
data presentation/data visualization	9	33.3
guidance on statistical software	7	25.9
data monitoring	7	25.9
protocol review	6	22.2
response to manuscript/publication reviewer	6	22.2
questionnaire design	5	18.5
protocol development	5	18.5
collection of data	4	14.8
data interpretation	4	14.8
survey design	4	14.8
interpretation of statistical methods	3	11.1
application of statistical methods	3	11.1
sampling design	3	11.1
development of specialized statistical methods	3	11.1
multivariate modeling	3	11.1
model fitting	3	11.1
randomization schemes	3	11.1
database creation	3	11.1
survey analysis/data	3	11.1
Bioinformatics	2	7.4
IRB submission/resubmission	2	7.4
paper reviews	2	7.4
trial design	1	3.7
study conduct	1	3.7
Survival analysis	1	3.7
mixed modeling	1	3.7
hypothesis testing	1	3.7
Inferential statistical analysis	1	3.7

which the responder would try to improve in the future. The questionnaire in Japanese can be viewed online (https://sites.google.com/site/biostatncgmjp/project-4), and its English version is provided as an appendix to this paper.

3. Results and Discussion

Among 15 biostatistical units in each research center or hospital, 14 units responded to the survey (response rate : 93.3%). Out of these 14 statistical units 8 units are affiliated with the national or public university, 3 units are affiliated with the private university, and 3 of them are the national advanced medical research centers. All 14 units provide biostatistical consultation, and half of them affiliated with national or private university offer consulting both internally and externally, and the other half of them offer only internal consultation.

3.1 Who provide statistical consultations to Whom?

The total number of staff for biostatistical consultation is 1-3 in 12 out of 14 statistical units. Only other 2 units (14.3%) affiliated with the private or public university have a middle size unit (4-10 staffs). There is no larger size unit with more than 10 staff which is observed in the North American or European countries. For reference, in 1995 in the

Table 3 Type of staff member for biostatistical consulting in each clinical center/hospital

	Type of staff member	Number of units with employee (s) in category	(%)
National advanced medical centers (n=3)	Professor level (Director)	1	1/3 (33)
	Associate professor level (Chief)	1	1/3 (33)
	Assistant professor/Post doctorate level (Research scientists)	2	2/3 (66)
Universities (n=11)	Professor level	5	5/11 (45)
	Associate professor level	7	7/11 (64)
	Assistant professor level	8	8/11 (73)
	Student	1	1/11 (9)
	Medical Doctor	2	2/11 (18)

Table 4 Number of consulting cases per month by unit size

Unit size	Number of consulting cases per a month 2-3	4-7	8-15	>15
1	1	0	2	1
2-3	1	3	4	0
4-10	1	0	0	1
(n=14)	3 (21%)	3 (21%)	6 (43%)	2 (14%)

United States, it is reported that 17 out of 31 (54.8%) biostatistical units employed more than 10 staff members.[12] In German paper in 2007,[14] 63% or consulting units in medical institutes were categorized into 'large unit', which was defined as those who employed more than one chair or single chair with a number of lecturers/senior lectures. **Table 3** shows the type of staff member in biostatistical consulting units. 79% units are organized with at least one senior (associate professor/professor) level statistician. Compared to the results of the survey in the North America in 1995,[12] it is distinct that the Masters/Bachelors level biostatisticians are not much employed in each section/unit and there are still clinical centers in which medical doctors are conducting statistical consultation. Additionally only one unit provide an opportunity for students to take part in biostatistical consulting activity although most of centers are affiliated with the university.

We also asked to whom statistical consultation is offered. Among 7 units which offer not only internal but also external consultation, 5 (71%) units offered only for researchers and students affiliated with academic institutes and another 2 units offered not only for people affiliated with academic institutes but also for people affiliated with industry for free. Details about the results and discussion of fee for consultation is described in section 3.4.

3.2 How statistical consulting provided?

All units offered face-to-face oral consulting and 12 (86%) units offered e-mail consulting. Furthermore, 7 (50%) units offered telephone consulting. Only 1 unit offered online consulting, for which would be expected to increase demand with the developments in information technology.

We asked the time spent on a consultancy case by a multiple choice question with the outcomes 15 min, 30 min, 1 hour, 2 hours and not-determined. 64% of the cases needed more than 1 hour, which observation is almost the same as the results of the survey in German medical schools.[14] Another 36% of the units responded that the time for consultation was not determined.

We also question the number of requests received in a categorical scale with outcomes every day, a few times per a week, once in a week, a few times per month, once in a month, once in a half year and once in a year. **Table 4** shows the number of consulting cases are not associated with the unit size and the marginal distribution of number of consulting cases per month was almost the same as the numbers shown in German survey. Hence, it is suggested that statistical consulting would not be organized properly appropriate for the number of researchers in each institute and the total amount of grant that are awarded during a year. Furthermore, taking the results described in Section 3.1 together, the average number of cases per consultant per month in Japan would be relatively large compared to those

Table 5 Area or subjects for biostatistical consultation

area/subjects for consultation	number of units	(%)
Study Planning Phase		
Study plannning/Study design/Protocol development	13	92.9
Sample size/Power analysis	13	92.9
IRB submission/resubmission	9	64.3
Protocol review	9	64.3
Statistical Aanalysis Plan/Documantation for statistical analysis	8	57.1
Grant application/proposal	7	50.0
Reporting Phase		
Data analysis	13	92.9
Report/publication writing/manuscript preparation	12	85.7
Response to manuscript/publication reviewer	12	85.7
Others		
Paper reviews	8	57.1
Data management	6	42.9
Programming	6	42.9
Simulation	4	28.6
Grant reviews	4	28.6
Data presentation/Data visualization	2	14.3

in Germany and the North America.

3.3 Area and subject of statistical consulting

As we mentioned in Section 2, a list of subjects for statistical consultation was made based on the result in **Table 2** and personal communication with some Japanese statisticians. **Table 5** shows that the major subjects of statistical consultation in Japan are apparently the same as those in other countries. According to the additional question, however, 100% units offered not only statistical "consultation" but also statistical practice within the framework of statistical consultation. In German, 89% of statistical consulting units in Medical science offered only oral consulting and only other 11% offered oral consulting including statistical analysis.[14] Hence biostatistical consulting in Japan implies pursuing or helping with the analysis of data and it is suggested that contents of statistical consultation in Japan would be different from those in other countries even in the same area or topics.

3.4 Fee for consultation

We did not ask much about financial aspects of a statistical consulting but just asked if the sections/units charged for internal or external consulting service. 57% units offered only free consulting service, and the other 43% units charged for external or internal consultation, however, all of them answered that the consulting fee depends on the situation, which implies they seem not to have a fee schedule for their consulting service, or it does not work even if it exists. It could be therefore no unit answered specifying fee for consulting in the unit.

3.5 Consultation leads to collaborative studies?

We also question whether consultation leads to collaborative studies and a chance to get co-authorship because the discussion in Niland's paper[12] and our experience show that it is statisticians' big concern. 4 (29%) units answered that statistical consultation lead little chance to get collaborative project and another 10 (71%) units answered statistical consultation lead only collaborative studies without payment (5 units) or granted collaborative studies in which statisticians could participate in one of investigator (5 units). We should note that we did not ask if statistical co-authorship was received routinely. It is described in Niland's paper that "the investigator is sometimes less likely to extend co-authorship when biostatisticians bill for their time and effort." Additionally, "it was suggested that only time spent in more routine tasks such as data entry and programming be charged back to investigators, and more conceptual activities such as proposal design, grant, and manuscript preparation be provided without charge to maintain a collegial relationship with investigators." It would be suspected that many present Japanese

biostatisticians would be suffering from a similar situation back in 90s in the United States. According to the International Committee of Medical Journal Editors (http://www.icmje.org) : "All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Authorship credit should be based only on :

①a) substantial contributions to conception and design or
b) acquisition of data or
c) analysis and interpretation of the data
②a) drafting of the article or
b) revising it critically for important intellectual detail
③a) final approval of the version to be published.

Conditions 1, 2, and 3 must all be met."

Based on the guideline like above mentioned, now some American institutes issue a guideline for determining co-authorship for biostatisticians. It is suggested that biostatistician need to know what is the authorship and to be trained how to collaborate with investigators to be an author of a scientific paper as well as investigators are need to be educated how to collaborate with biostatisticians.

3.6 Consulting is used as practical training?

Described in Section 1, it has been well debated that statistical consultation is effective for understanding of statistics and practical skills in statistics. In German,[14] 21% of the units in Medical science departments included internal consulting cases in the curriculum. However, in our survey, there was no institute which used statistical consulting as practical training for junior biostatisticians. As described in Section 3.1, there was only one unit in which a student joined as a consultant, suggesting that there would be few institutes which utilize statistical consulting for education. However, the corresponding questionnaire item does not ask clearly about the educational use of statistical consulting for students cooperated with the university, so it would be future work to assess educational use of statistical consultation in more detail.

3.7 Concerns of statisticians

Finally we question whether the statisticians have some concerns about biostatistical consultation. The answers from 7 units are summarized as follows.

1) Almost works for consultation are doing without any instructions or regulations.
2) Staffing problem (especially for shortage of manpower)
3) Funding issues

Regarding the issue 1), this problem which could be originated in Japanese fuzziness culture would be a big problem especially in academic institutes not only for work for consultation but also for any work in clinical research. Someone is doing something somehow to someone makes sometimes a critical mistake. Additionally, time and effort are not usually explicitly regulated and allocated for biostatisticians by the universities or research institutes. Currently some institutes in other countries issue guidelines for estimating biostatistician effort. For example, it is clearly mentioned in the guidelines of University of California Davis School of Medicine[15] that "We strongly recommend that biostatisticians be actively involved throughout the grant proposal development process," and "In general, funding for faculty and staff should not fall below 10% of total effort per statistician per time period on a single project. Although there occasionally are valid reasons for a lower level of effort on particular projects, intervals with funded effort falling below 10% require approval by the division chief for faculty and by the CTSC* biostatistics director for CTSC staff." Furthermore, effort is allocated by the size of projects and the level of statisticians in the guidelines. Prompt attention to this issue should be made in each institute, and it is desirable to develop a guidelines for biostatistician effort or/and a working instruction for biostatistical consultation based on experience in the initiative institutes with sufficient experience in biostatistical consulting.

It has been well debated for concerns in the issue 2) and 3) in Niland et al.[12] and other papers.[1,6,7,9] From those discussions, consultation units especially in the United States have been changing their approach and structures. At present in Japan, staffing concern was almost limited to shortage of manpower, however, like as in the United States, it could be substantially developed for shortage of appropriate level of statisticians along with the increase of demand for consultation for advanced statistical problems with popularization and improve-

*CTSC : Clinical and Translational Science Center

ments of curriculums in Biostatistics in medical schools in near future.

As concerns in funding, careful considerations would be needed to compare discussions especially in the United States with our concerns because budget size for research and its funding structure in Japan is so different from those in the United States, although which has been dynamically changing due to economic crises.[16,17] Concerns in funding have inextricable link between the deep-rooted problems in research funding structure in Japan, such as unequally-distributed research funding at the institution and individual levels.[18] One of the reason why statistical consulting units are not funded or do not charge for consultation would be that many clinical research themselves are not well funded.[19] It should be a great difficulty to have a fundamental change in such funding structure in Japan, while each unit could clarify the utility of statistical consultation to some extent to make clear the contents and the time consumed for consultation.

4. Conclusion, study limitation and future research implications

Our survey provided a first view of biostatistical consulting activity in Japanese medical institutes, from which information is likely to be of interest both to biostatisticians (consultees) and medical or clinical researchers (consulters). It is suggested that the subjects for statistical consultation are similar but its contents and work environments for consultants in Japan would be much different from those in other countries, especially from those in the United States. Additionally, the current concerns about biostatistical consultation in Japan are almost the same as those in the United States discussed 20 year ago (e. g. in Niland et al.[12]). The culture of consulting seems to be weakly developed for biostatistical sections in Japan, while the biostatisticians is likely to feel overloaded with the work not so much consultant as data analyst.

There are some limitations of this study. First, our survey could not be complete census of the population we assumed. It is possible that we did not get information for some biostatistical units in medical research institutes because we could not get the list of all biostatistical units in Japan which was publicly available such as a list of America Statistical Association on the website, however, the biostatistical units in Japanese representative medical research institute were included in our survey. Additionally, our survey population does not include biostatisticians who are working in the medical university or other educational departments, such as department of public health, pharmacology or engineering. It would be expected that the results of our survey could be devastating if such populations were included, because, to our knowledge, most of departments in Japanese university do not have any system and evaluation standards for statistical consultation. It is very hard to recognize and survey such latent biostatisticians. To study on such population, we would expect that our research would activate serious discussion about statistical consulting among Japanese statistical associations or other formal organizations.

As we mentioned in the result section, we did not ask much about the topic of funding issues because we considered Japanese were very sensitive to the question about money issues. Our survey showed that more than half of units offered only free consulting service. However, the topic of consulting fees, including factors making up budgets and methods of billing, often comes up in discussion among statistical consultants,[13] and it is important to clarify especially for the unit without any consulting fee about how the unit is organized and how much it costs to keep biostatistical consultation for a certain medical research institute. Further investigation would be needed for this topic.

According to the report released from Ministry of Health, Labour and Welfare in 2006,[20] only 9 out of 346 institutes or hospitals employed biostatistician, and the average number of biostatistician per institute was reported as about only 1 for the university hospital ($n=4$). Compared to the content of the discussion in the report with our results, we might say that the number of institute with biostatisticians is increased and the demand for biostatisticians has been rapidly increasing compared to 8 years ago, however, the number of biostatisticians per one institute is not increased. Additionally, our survey suggested that the concern of biostatisticians is not so changed and working environment for biostatisticians in medical institutes would not be so improved during the last 7 years. Biostatistical consulting activities in Japanese medical institutes or research hospitals have only just begun. We believe our results will be of some help to develop and promote statistical consulting activities in Japanese medical institutes.

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Appendix：
A questionnaire survey about biostatistical consultation service (in English)

Let's answer!

This questionnaire survey is being taken in order to better understand the actual state of biostatistical consultation services in the Japanese academia, and also to serve as materials for discussions on what types of services shall be provided in the future. The result of the survey is scheduled to be reported to statistics-related societies and journals, while keeping the information on individual institutions confidential upon obtaining your agreement.

We would be grateful if you could answer all the questions in this questionnaire, and greatly appreciate for your understanding and cooperation.

Q1
Which one of the following categories applies to the institution that the respondent is affiliated with?

- National or Public university
- Private university
- National advanced medical research center
- etc.

Q2
Please specify your primary affiliation.

Q3
Biostatistical consultation services being：

- Provided externally as well as internally by the institution.
- Provided only internally, as public services of the institution.
- Provided only internally, by tacit understanding.
- Not provided at present, but I would like to see it provided in the future.
- Not provided at present, nor do I want to see it provided in the future.

If you answered "Provided" to Q3, please answer Q4. If you answered "Not provided" to Q3, please skip Q4-Q17 and continue from Q18.

Q4
Biostatistical consultation is being provided to (Please check all that apply)：

- Doctors and/or researchers affiliated with the institution
- Doctors and/or researchers affiliated with the mother institution
- Students affiliated with the institution
- Students affiliated with the mother institution
- Associates of doctors and/or researchers affiliated with the institution
- Associates of doctors and/or researchers affiliated with the mother institution
- Associates of students affiliated with the institution
- Associates of students affiliated with the mother institution
- Doctors and/or researchers not affiliated with the institution
- Students not affiliated with the institution
- Biostatisticians not affiliated with the institution
- Corporate doctors and/or researchers
- Corporate Biostatisticians

NOTE：

1) *"The mother institution," means, for example, in case of a university, the entire university, including academic departments, laboratories, centers, and any other institutions affiliated with the university.*
2) *"Associates" refer to collaborators and companions.*

Q5
Please choose the type of consultation being provided. (Please check all that apply)
- ◦ Consultation related to research planning
- ◦ Consultation related to grant application
- ◦ Actual work related to grant application
- ◦ Consultation related to study protocol application
- ◦ Actual work related to study protocol application
- ◦ Consultation related to sample size estimation
- ◦ Actual work related to sample size estimation
- ◦ Consultation related to statistical simulation studies
- ◦ Actual work related to statistical simulation studies
- ◦ Consultation related to working instructions for data management
- ◦ Actual work related to working instructions for data management
- ◦ Consultation related to statistical analysis plans
- ◦ Actual work related to statistical analysis plans
- ◦ Consultation related to preparation of working instructions for statistical analysis
- ◦ Actual work related to preparation of working instructions for statistical analysis
- ◦ Consultation related to analytical programming
- ◦ Actual work related to analytical programming
- ◦ Consultation related to statistical analysis (other than programming)
- ◦ Actual work related to statistical analysis (other than programming)
- ◦ Support for manuscript writing
- ◦ Consultation for data visualization
- ◦ Support for data visualization
- ◦ Support for, and actual work on, making replies to the reviewers
- ◦ Grant review
- ◦ Protocol review
- ◦ Review for manuscripts
- ◦ Others

Q6
If you selected "Others" in Q5, please state specifically as to what other work is being conducted.

Q7
What is the usual development after the first consultation session is provided?
- ◦ Consultation ends after the first session.
- ◦ Consultation ends after the second session.
- ◦ Consultation continues through the third session or longer.
- ◦ It turns into a volunteering-like joint research project.
- ◦ It turns into a revenue-generating joint research project such as role-divided research.

Q8
Please select who is providing the consultation.
- ◦ Professor level Biostatisticians
- ◦ Associate Professors level Biostatisticians
- ◦ Assistant Professor level Biostatisticians
- ◦ Master or under level biostatisticians
- ◦ Students in the department of biostatistics
- ◦ Other students
- ◦ Medical doctors
- ◦ Statisticians
- ◦ Others

Q9
Please select an applicable category related to the time length of a consultation session.
- 15 minutes
- 30 minutes
- 1 hour
- 2 hour
- 3 hours or longer
- No set time length

Q10
Please select the consultation method being used. (Please check all that apply)
- Face-to-face
- Telephone
- Web (Internet)
- e-mail
- Others

Q11
If you selected "Others" in Q10, please state specifically as to what other consultation methods are being used.

Q12
Please select the frequency of consultation being provided.
- Almost every day
- Twice to three times a week
- Approx. once a week
- Approx. twice to three times a month
- Approx. once a month
- Approx. once every six months
- Approx. once a year

Q13
Please select the number of staffs that are providing consultation in your section.
- One
- Two persons
- Three persons
- More than three persons but less than 10 persons
- More than 10 persons

Q14
Please select the fee structure of consultation.
- Free consultation in all cases.
- Free consultation for any client for the first session, paid consultation from the second session.
- Free consultation for any client for the first session, paid consultation from the second session for external clients (internal clients need not pay).
- Internal clients need not pay in all cases. External clients must pay from the first session.
- All clients must pay from the first session.
- Depends on the case.

Q15
If you selected "Depends on the case." in Q14, please state specifically as to what kind of fee setting is being used.

Q16
Is consultation-related training being offered to statisticians?
- Yes
- No

Q17
If there is any issue related to consultation services being provided by your institution, please let us know.

Q18
If there are any biostatistical consultation services you would like to enhance, please list them.

Q19
This question is only intended for the respondents that stated that there are no biostatistical consultation services being provided. Please state specifically as to why that may be the case.

Q20
Please select from the following concerning the publication of the aggregated result of this questionnaire survey.
- I consent to publication through presentation at academic societies and publication in a scientific journal.
- I only consent to publication through presentation at academic societies.
- I only consent to publication in a scientific journal.
- I do not consent to publication of any sort.

Please submit!

Q17 臨床試験・治験とは？

A 「人」を対象として何らかの実験的介入（治療・診断・看護ケア・予防等）を加えてそのアウトカム（結果）を評価する「介入研究」のうち，介入の単位が個人であるものを「臨床試験」と言う（介入の単位が地域や職場である場合は「地域介入研究／職場介入研究」と呼ぶ）。

臨床試験のうち，厚生労働省から医薬品や医療機器の製造販売承認を得ることを目的として行うものを「治験」と呼ぶ（「臨床治験」と言う人がいるが何を指すか明確でなく使うべきではない）。

治験には企業主導治験と（2003年の薬事法改正により可能となった）医師主導治験があり，企業主導の治験や製造販売後臨床試験以外の医療者／研究者による臨床試験を「研究者主導臨床試験」と呼ぶ。後者は長いので単に「臨床研究」と呼ばれることがあるが，本来の「臨床研究」は「介入研究」と「観察研究」を含む広い概念（治験を含む概念）なので治験の対義語として使うのは正しくない。短く呼ぶなら英語の「investigator-initiated trial」の略の「IIT（アイアイティー）」がよいと思われる。

治療についての臨床試験は「治療開発」を目的として行われるが，治療開発は「相（phase）」と呼ばれる段階を踏んで漸踏み的に行うべきという考えが国際的なコンセンサスである。一般に医薬品開発の「相」が，以下の第Ⅰ相～第Ⅳ相とされているが，考え方は医療機器，手術手技，放射線治療，集学的治療の開発も同じである。

第Ⅰ相：人に安全に投与／実施できるかどうかを探索する段階
第Ⅱ相：当該疾患（対象集団）に対する有効性があるかどうかを探索する段階
第Ⅲ相：標準治療よりも良い治療であるかどうかを通常はランダム化比較試験にて検証する段階
第Ⅳ相：市販後の日常診療で広く使われて初めてわかるような，長期投与による毒性（時に有効性も）や稀な毒性を調べる段階

本来，治療開発の「相」と各相で行われる試験の「種類（type）」は別の概念だが，「がん」の治療開発においては第Ⅰ相で臨床薬理試験を行って推奨用量を決定し，第Ⅱ相でがん種を特定して有効性を探索し，第Ⅲ相でランダム化比較試験による検証を行うことが定形化されているので，試験名として「第Ⅰ相試験」，「第Ⅱ相試験」，「第Ⅲ相試験」と呼ぶことが一般的になっている（他の疾患領域では必ずしもそうではないことに注意が必要）。

臨床試験においてアウトカムを測る「ものさし」を「エンドポイント（endpoint）」と呼び，各

試験で試験の結論を下すのに一義的に用いられるエンドポイントを主たるエンドポイント（primary endpoint）と呼ぶ。

第Ⅰ相試験では用量制限毒性（dose limiting toxicity：DLT），第Ⅱ相試験では奏効割合，第Ⅲ相試験では全生存期間（overall survival：OS），無再発生存期間（relapse-free survival：RFS），無増悪生存期間（progression-free survival：PFS）等がprimary endpointとされることが一般的だが，手術の第Ⅱ相試験で治癒切除割合を用いたり，奏効割合がエンドポイントとして適切でない分子標的薬の第Ⅱ相試験でランダム化第Ⅱ相試験としてPFSを用いたり，試験の対象や治療の特性によって適切なエンドポイントが選択される。

（福田 治彦）

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特集 免疫療法の逆襲を現実化した免疫checkpointの修飾

免疫療法の臨床評価に関する問題点*

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Key Words：immune-checkpoint inhibitors, FDA guidance, Fleming-Harrington test, immune-related Response Criteria

はじめに

2011年に抗CTLA-4抗体であるipilimumabが米国で承認され，2014年7月に抗PD-1抗体であるnivolumabが日本で承認されるなど，免疫チェックポイント阻害薬が現実に実臨床に導入される時代がやってきた．今後もさらに多くの免疫治療薬の開発が進むことが期待されるが，迅速に臨床現場に導入されるためには臨床試験による正しい評価が欠かせない．一方で，免疫療法はその作用機序から，治療後の一時的な腫瘍増大や，その後の腫瘍縮小など独特の効き方が観察されることが知られており，その点を考慮に入れた臨床評価法が提唱されている．

本稿ではがんワクチンの評価について書かれたFood and Drug Administration(FDA)ガイダンスの枠組みを用いてphaseごとの免疫療法の臨床試験デザインの考え方を紹介するとともに，近年免疫療法の領域で見かけるようになったFleming-Harrington検定，そしてimmune-related Response Criteria(irRC)の考え方と問題点について述べたい．

がんワクチンについてのFDAガイダンス

2009年にFDAの生物製剤部門であるCenter for Biologics Evaluation and Research(CBER)は，製薬企業向けのがんワクチン評価のガイダンス“Guidance for Industry- Clinical Considerations for Therapeutic Cancer Vaccines”の「案」を公表し，その後2011年に正式に公表した[1]．がんワクチンが抗腫瘍効果を発揮するための一連の免疫応答には一定の時間を要するため，効果の発現までがこれまでの抗がん剤より遅くなるという特徴があり，そのために臨床試験のデザインにも従来の抗がん剤とは異なる考え方が必要になるということが，このガイダンスが出された背景にある．免疫チェックポイント阻害薬のようなリンパ球の表面分子群をターゲットとするような薬剤は，がんワクチンとは異なる作用機序を有することからこのFDAガイダンスの対象外とされているが，免疫チェックポイント阻害薬でも同様に抗腫瘍効果の発現が遅れて現れる現象が知られており[2]，デザイン自体の考え方には参考となる記述が多い．以下にガイダンスで述べられている各phaseのデザイン上の留意点を，

* Methodological issues in clinical trials of cancer immunotherapy.

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私見を交えつつ概説する．

1．Phase I

免疫療法のphase I試験であっても，従来のいわゆる3例コホートによる用量探索が行われる．しかし免疫療法ではdose-response curveやdose-toxicity curveが必ずしも直線的ではなく一定の用量を越えた段階でフラットになるため，多くの例で最大耐用量(MTD)に達しないことが多い．そのため3例コホートを用いた方法はがんワクチンの評価に最適とは限らない．Accelerated titration methodやcontinuous reassessment methodといったデザインも考えられるが，どのようなデザインを採用するにせよ重要なのは用量制限毒性(DLT)，治療中止規準，試験の中止規準をプロトコールに明確に定義することである．また，DLTが観察されないことが予想される場合や実際に観察されない場合には，免疫応答が確認されたかどうかといった他のエンドポイントにより用量を決定することが有用なことがある．ここまでがFDAガイダンスに述べられていることである．

実際dose-toxicity curveが直線的ではなく，一定の用量を越えるとプラトーに達するという現象は分子標的薬等でもみられることである．ただし，実際には用量探索というよりも安全性の確認や免疫応答の確認を行うという目的とあわせてシンプルな3例コホートが採用されていることが多いようである．Accelerated titration methodとcontinuous reassessment methodは，いずれも効果が期待できる用量まで早めに用量レベルを上げていくデザインであるが，それらを採用したからといって本質的にはdose-toxicity curveがフラットになる場合に上手く最適用量を決定できるわけではない(いずれも毒性をアウトカムとして次患者の用量を決定していくが，毒性が生じなければMTDという意味での用量を決めようがない)．実際には用量と毒性が比例関係にない場合にはphase I段階の少数例で最適用量を決定することは難しく，最適用量の決定はphase IIやphase IIIに持ち越される例もみられる．たとえばstage IIIBC期IV期の悪性黒色腫に対するipilimumabの術後補助化学療法のphase III試験であるECOG1609は，標準治療群であるインターフェロンα2b群に対して，低用量ipilimumab(3 mg/kg)，高用量ipilimumab(10 mg/kg)と2つの試験治療群が設定された3群試験であった(ClinicalTrials.gov：NCT0127433)．Phase IIIとまでは行かなくとも有効性をアウトカムとしたrandomized phase II等の段階を経ないと最適な用量が決めがたいということは，dose-toxicity curveが比例関係にない薬剤の難しい点である．ただし，phase Iで用量が決まらない，あるいは，用量を決めるためにランダム化を行うといったケースは，抗がん剤の開発では稀であるものの，通常の医薬品の開発においては当たり前に行われていることであり，免疫療法の治療開発が特殊なのではないことにも注意が必要である．免疫療法の開発に必要な臨床試験の方法論が難しい・特殊なのではなく，逆に抗がん剤の開発に必要な方法論が他の薬効領域のものに比べて単純であったにすぎない．必要なことは，抗がん剤との差異に拘泥することではなく，他の薬効領域の薬で当たり前に行われていることを当たり前に行うこと，科学的に開発を進めることである．

2．Phase II

FDAガイダンスではphase II試験をsingle-armで行う場合と，randomizeして行う場合のメリット，デメリットをあげている．

Single-armで奏効割合をprimary endpointとするのが伝統的なphase IIデザインであったが，免疫療法はそもそも早期に腫瘍縮小効果が得られにくいため，奏効割合をエンドポイントとしたスクリーニングは適切とはいえない．とはいえ，全生存期間や無増悪生存期間といったtime-to-event型のエンドポイントをヒストリカルコントロールと比較することが良いともいえない．なぜなら，これらのエンドポイントはselection biasの影響を(奏効割合よりも)受けやすく，支持療法の進歩など，介入以外の要素の影響を受けるからである．これは免疫療法に限った話ではなく，やむを得ない事情がない限り，single-armの試験でtime-to-event型のエンドポイントをprimary endpointとすることは，筆者の所属するJCOGデータセンター/運営事務局でも推奨していない．

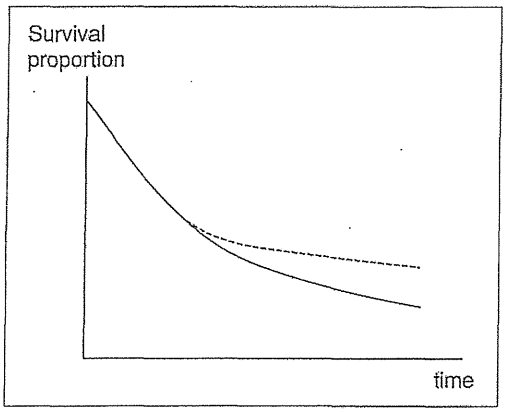

図1　Delayed effectがある場合の生存曲線

こうしたselection biasや支持療法の進歩の影響を排除しうるのがrandomized phase II 試験デザインである．ランダム化によりこれらのバイアスを排除しうるため，比較可能性の観点からはsingle-armより利点が多い．サンプルサイズがsingle-armよりは一般に多くなり結果が得られるまでに時間を要することが欠点といえば欠点であるが，single-armの試験には前述のように問題が多く，特にlate phase II の段階では今後randomized phase II デザインがさまざまな場面で頻用されていくことが予想される．なお，先述の用量設定と同様に，通常の医薬品開発においてsingle-armのphase II 試験を行うことの方がむしろ珍しいのであって，免疫療法の開発のためだけに特殊な方法論が必要なのではなく，通常の医薬品開発の常識を適用する必要があるにすぎないという現実も，われわれ臨床試験に携わる研究者は理解しておくべきである．

FDAガイダンスではsingle-armかrandomized designのいずれかを推奨するかは明確に書かれておらず，考え方のみ示されている．これは推奨されるデザインが試験の目的によって変わりうるからであろう．たとえば免疫学的効果を有するかどうかといったproof of conceptを確かめたい場合にはsingle-armで十分な場合もあるだろうし，比較可能性を高めて次のphase III へ進めるかどうかのスクリーニングをしたいのであればrandomized designが推奨されるといった具合である．Randomized phase II 試験デザインの種類と方法の詳細については他稿を参照されたい[3]．

3．Phase III

FDAガイドラインでは，phase III 試験の場合のエンドポイントについて特別な言及は行っておらず，従来の薬剤を対象としたエンドポイントについての各種のFDAガイドラインを参照するよう記載している．すなわち薬剤の承認に必要なのは，患者のベネフィットを反映したエンドポイントである全生存期間の延長や症状改善効果，あるいは，確立されたsurrogate endpointにおける有効性が示されることである．エンドポイントとは「患者のベネフィットを測るものさし」であり，患者のベネフィットは免疫療法であろうが他の治療法であろうが変わるものではないので，免疫療法のために特別なphase III のエンドポイントが用意されるわけではない，というのは当然であろう．

ただし，FDAガイドラインでは免疫療法において，delayed effect（治療開始直後のearly progressionがみられ，その後に効果がみられる現象）を考慮に入れる必要があることを述べている．delayed effectがみられた場合，2群の生存曲線は早期ではほとんど変わらないものの，一定の期間を経た晩期に生存曲線が離れだすような形をとることになる（図1）．このような場合には晩期に効果があったとしても全体としては効果が薄まってしまうので，その分サンプルサイズを増やしたり，十分な観察期間ののちに主たる解析を行ったりするような工夫が必要であると述べている．また，主たる解析の方法を選択する際には比例ハザード性が成り立たない場合があることも考慮すべきとしている（なお，Cox回帰分析は比例ハザード性を前提としているが，ログランク検定や後述するFleming-Harrington検定は比例ハザード性を前提としていない）．

免疫療法の生存時間解析

さて，FDAガイドラインでは免疫療法のdelayed effectを考慮に入れてサンプルサイズを増やしたり，十分な観察期間を置くことが推奨されているが，delayed effectをより鋭敏に検出するためにFleming-Harrington検定という生存時間解析法が用いられる場合があり，日本免疫治療学研究会と日本バイオセラピィ学会がそれぞれ公表し

ている免疫療法の臨床評価に関するガイダンスでも取り上げられている[4)5)]．

通常のログランク検定ではイベントが生じた時点ごとに「2群の生存期間に差はない」という帰無仮説からのズレを計算し，すべてのイベント発生時点のズレを合計するという手順をとる．この合計を行う際，ログランク検定では早期にイベントが生じようが晩期にイベントが生じようが，各イベントの重みを同等に扱っている．これに対して一般化Wilcoxon検定ではイベント発生時点でのリスク集合(number at risk)を重みとしてかけることになるので，リスク集合が多い早期のイベントが重く扱われることになる(早期に生存曲線が開いていれば有意になりやすくなる)．これに対してFleming-Harrington検定での重みは表1のように表される．ここで$S(t_{(f-1)})$は，ほぼその時点での生存割合を意味することから，pを大きくすれば早期のイベントを重視することになり，qを大きくすれば晩期のイベントを重視することになる．免疫療法ではdelayed effectを検出するために晩期のイベントを重視するようにp,qを設定することになるが，pやqは任意のパラメータであるため，決め方に一定のルールがあるわけではない．これらは恣意的になることがないように事前にプロトコールに定めておく必要がある．

なお，Fleming-Harrington検定はプラセボに比べ免疫療法に「薬効があるかどうか」を確かめる際の検出力を高める方法としては有用であるが，従来の標準治療と比べて免疫療法が「新たな標準治療(すなわち，適格規準を満たす患者に対して第一選択として推奨すべき治療)となるかどうか」を決める場合に常に有用といえるか否かは自明ではなく，注意が必要である．一般にあいまいにされているが，ある治療法に薬効が存在するか否かを判断することと，その治療法の効果が第一選択として推奨すべきものであるか否かを判断することとは別の問題である．そもそもFleming-Harrington検定は晩期のイベントの重みを重要視しているわけであるが，エンドポイントが「患者のベネフィットを測るものさし」であるとすれば，治療を受ける前にその患者が早期に死亡するのか晩期に死亡するのかの区別がつかない状況であることも考え合わせると，患者にとって早期の死亡と晩期の死亡のどちらがより意味があるか，という問いに答えを出すことは困難なはずである(あったとしてもそれは個々の患者の人生哲学によるものであろう)．言い換えると，ログランク検定では「どの時点で死亡しようがとにかく死ぬのはイヤ(死亡はすべて同じ重みとして扱う)」と考えるわけであるが，Fleming-Harrington検定は「先に死ぬのもイヤだが後で死ぬのはもっとイヤ(晩期の死亡をより重大と扱う)」と考えて，しかもどれほど晩期の死亡に重みをつけるかは試験ごとに変えていることになる(重みは前述のp,qの設定に依存する)．患者の観点からすれば，(治療の特性によらず)どの時点であっても死ぬのはイヤと考えるのが自然であろうし，評価者の観点としても治療の特性が異なる場合に，時期によって死亡の重みに軽重をつけて治療の優劣をつけるという考え方は受け入れがたいのではないだろうか．もちろん，人の価値観はさまざまであるので，人によっては早期の死亡により重きを置くかもしれないし，人によっては逆に晩期の死亡に重きを置くかもしれない．とはいえ，早期の死亡により重きを置く人もいるかもしれないという状況がありながら一般化Wilcoxon検定ではなくログランク検定が用いられるのと同様の意味合いにおいて，一定の臨床的な条件を満たす集団に対する第一選択としての標準治療を評価するという観点からはログランク検定を用いることが適当であると筆者らは考える．

また，生存曲線が図2のような場合にはFleming-Harrington検定は有用であるが，図2のように生存曲線がクロスするような場合には少々ややこしいことになる．つまりログランク検定ではどの時点でのイベントも同等に扱われることから当然「差がない」という結論になるだろうが，

表1 検定手法ごとのイベントの重み付け

検定手法	重み
Logrank検定	1
Wilcoxon検定	n_f
Fleming-Harrington検定	$S(t_{(f-1)})^p \times [1-S(t_{(f-1)})]^q$ $p \geqq 0, q \geqq 0$

n_f：f番目のイベントが生じた時点でのリスク集合の数，
$S(t_{(f-1)})$：f-1番目のイベントが生じた時点での生存割合．

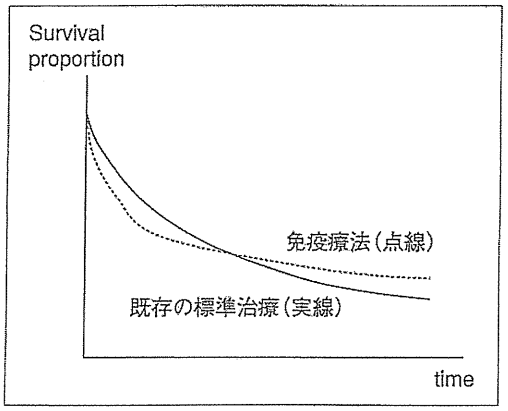

図2　生存曲線がクロスする場合の解釈

Fleming-Harrington検定の場合には晩期のイベントを重視することから「免疫療法が良い」という結論になる可能性がある．生存曲線がクロスするような場合には，ベネフィットを受けるサブグループが存在しそうかをみるといったサブグループ解析を含めてさまざまな角度から結果を解釈する必要があるにせよ，このようなクロスした生存曲線を見せられて「免疫療法の方が良い」と判断する臨床医は多くないであろう．検定方法は，こうした臨床医の意思決定と検定結果ができるだけ一致するような手法が望ましい(統計的検定に基づく判定結果と臨床的判断とに乖離があるようでは，意思決定ルールとして最適とは言いがたい)．従来の薬剤を用いた治療法が対照群となっている場合，こうした可能性も考慮に入れつつFleming-Harrington検定は慎重に適用する必要がある．その意味で，実際にFleming-Harrington検定が適用できるのは，プラセボと免疫療法の比較など，効果の発現タイミングがdelayed phaseに限って期待できる場合のみと考えられる．

Immune-related Response Criteria(irRC)

免疫療法のdelayed effectを効果判定に取り入れるべく，2009年にWolchokらは新たな効果判定規準であるimmune-related Response Criteria(irRC)を提唱した[2]．これは現在のスタンダードであるRECISTや，旧来のWHO規準とも異なる効果判定規準であり，ipilimumabのphase II試験において，早期の増悪がみられたあとに腫瘍縮小効果がみられた例や，新病変が出現したあとも治療を続けた結果，新病変が消失した例を正しく評価するために作成したとされている．このirRCとRECIST, WHO規準との違いを表2に示す．RECISTとirRCが大きく異なる点は，①治療開始後に出現した新病変を総腫瘍量に含めること，②治療開始後早期に新病変が出現しても総腫瘍量がprogressive disease(PD)規準を満たさなければPDとしないこと，③PDの判定に確定を要すること，の3点である．これらはすべてdelayed effectを評価するために行われた工夫であり一見魅力的な提案にみえるのであるが，実は方法論的にさまざまな問題点があり，そのまま採用することはおすすめできない．

irRCの問題点と代替案は別稿[6]に詳しいためそちらを参照いただきたいが，ここでは①効果判定規準と治療中止規準を混同している，②比較可能性について考慮されていない，という2点の問題点を指摘しておく．

効果判定規準とは，従来の薬剤と新規薬剤の有効性の比較を行うためのツールである．RECISTは治療間の奏効割合〔complete response(CR), partial response(PR)〕や無増悪生存期間(PD)を同じものさしで測定し「比較」するためにつくられた規準である．そのため，効果判定規準の第一の要件は「比較可能性」である．一方irRCは，early progressionの段階で治療を中止せずに，その後も治療を継続して効果判定を続けるために作られたものである．つまりirRCは「治療継続/中止規準」と「効果判定規準」の2つの側面を有することになる．

RECIST ver1.1(文献)には，「(RECISTは)個々の患者における治療継続の是非についての意思決定に用いられることを意図していない」と書かれており，RECISTは効果判定規準であって治療継続/中止規準ではないことが明記されている．そして重要なことは，irRCで取り入れられた新病変の総腫瘍量への組み入れやPDの確定といったロジックは，いずれも画像判定で増悪と判断された場合に免疫療法を継続するための「治療継続規準」としては適切であるが，だからといって，わざわざ新たな複雑な効果判定規準を設ける必

表2　irRC，WHO規準，RECISTの比較

	irRC	WHO規準	RECIST
測定方法	2方向測定		1方向測定
測定可能病変	≧5 mm×5 mm	規定なし	Ver1.0 ヘリカルCTで長径≧10 mm リンパ節病変に言及なし Ver1.1 腫瘍病変：長径≧10 mm リンパ節病変：短径≧15 mm
測定病変数	ベースライン 各臓器≦5病変 内臓病変≦10病変 皮膚病変≦5病変 新病変出現時に追加 各臓器≦5病変 内臓病変≦10病変 皮膚病変≦5病変	規定なし	Ver1.0 各臓器≦5病変 計≦10病変 Ver1.1 各臓器≦2病変 計≦5病変
腫瘍量	積和		径和
総合効果	総腫瘍量の変化で判定(新病変の径の積和も総腫瘍径に含める)	標的病変の効果と，非標的病変の効果(新病変含む)の組み合わせで総合効果を判定	標的病変，非標的病変，新病変の各効果の組み合わせで総合効果を判定
規準値	(ir)CR：すべての病変が消失 (ir)PR：ベースラインに比べて50%以上減少 (ir)SD：いずれにも該当しない (ir)PD：経過中の最小値に比べて25%以上増加		CR：すべての腫瘍病変が消失 PR：ベースラインに比べて30%以上減少 SD：いずれにも該当しない PD：経過中の最小値に比べて20%以上増加
確定を要する判定	irCR, irPR, irPD	CR, PR	CR, PR

然性には乏しいということである．

そもそも効果判定規準とは既存の治療と新規薬剤の有効性の比較を行うためのツールであるため，既存の薬剤でも適用しうる規準でないといけないが，従来の殺細胞性薬剤の場合に新病変を総腫瘍量に組み入れるとか，PDを確定するまで評価を続けるといった規定を設けることは臨床医と患者にとって受け入れがたい規定であろう．その意味では従来の薬剤との比較にirRCを用いることはあり得ない．

免疫療法同士の比較にirRCを用いることができる余地は残るが，それとて複雑な効果判定規準を用いなくとも従来のRECISTをmodifyすることで十分対応可能である．すなわち，治療開始後の一定期間(「landmark time」と呼ぶ)までに認められた腫瘍の増大あるいは新病変の出現はイベントとしないという「landmark method」を用いた無増悪生存期間を用いることでearly progressionをイベントにすることを避け，delayed effectを評価することは十分に可能である[6]．まとめると，irRCの基本的な考えは，あくまで「治療継続規準」としてプロトコールに取り入れることとし，効果判定規準としては従来のRECISTをmodifyした形を採用するのが免疫療法の評価の際には穏当であろう．

なお，前述のがんワクチンに関するFDAガイダンス[1]には，画像判定で増悪がみられたにもかかわらずプロトコール治療を継続する際には，どのような場合に治療継続を行うことが許容されるかの規準を明確にプロトコールに定めることを推奨しており，治療継続の例として以下のような条件を例示している(一部意訳)．

- 増悪に関する条件の他は，適格規準をすべて満たす．
- 用量制限毒性(DLT)が観察されておらず，治療によって生じた毒性がすべてベースラインのgradeに回復している．
- Performance statusが悪化していない．
- 有効な救済治療がない．
- 増悪による重篤な症状(例：脳転移)を緩和