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Original Article

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Comparison of international guidelines for early-phase clinical trials of cellular and gene therapy products

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ABSTRACT

Cellular and gene therapies (CGT) are promising fields that are bringing significant clinical benefits to patients by directly targeting the underlying cause of disease. In line with this trend, regulatory agencies in every country have been making efforts to accelerate CGT product development. For acceleration, it is necessary to increase the efficiency of clinical trials, thus the early-phase clinical trials for CGT products should be elaborate and productive. The guidelines of international regulatory agencies were compared and analyzed to examine the considerations for the design of early-phase CGT products. The guidelines described a safety evaluation, preliminary evidence of effectiveness gathering, dose exploration, and a feasibility assessment as common objectives of early-phase clinical trials for CGT products. In addition, the considerations for the design of early-phase CGT products included pretreatment effects and problems in the manufacturing and administration process. The guidelines also covered selection of a study population, control group/blinding, and dose/regimen planning. There were differences in the degree of detail, description, and the scope of the content covered by each guideline. The guideline published by FDA was the most specific. However, when compared with the previous guidelines for designing early-phase clinical trials for small molecules and biologics, the current guidelines need to be revised to suggest more detailed and practical principles and rules.

Keywords: Cell and Tissue-Based Therapy; Genetic Therapy; Guideline; Clinical Trial Protocol; Clinical Trial, Phase I; Clinical Trial, Phase II

INTRODUCTION

Cellular therapy and gene therapy (CGT) represent overlapping fields of biomedical research and treatment. These are also called advanced therapy medicinal products in Europe. Cellular therapy, which uses cells as the therapy, includes cellular immunotherapies, cancer vaccines, and other types of autologous and allogeneic cells for therapeutic indications. The most recently approved product by the Food and Drug Administration (FDA) is Allocord, which is an allogeneic cord blood hematopoietic progenitor cell therapy indicated for use in unrelated

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donor hematopoietic progenitor cell transplantation procedures. Gene therapy modifies or manipulates the expression of a gene to treat or cure disease. It includes plasmid DNA, viral vectors, bacterial vectors, human gene editing technology, and patient-derived cellular gene therapy products. Abecma (idecabtagene vicleucel) is a gene therapy recently approved by the FDA to treat adult patients with relapsed or refractory multiple myeloma [1]. Cellular and gene therapies are promising fields that are bringing significant clinical benefits to patients by directly targeting the underlying cause of disease and cover the treatment of various diseases such as cancer, genetic disorders, and rare diseases [2].

The global CGT market reached a value of nearly $4.39 billion in 2020, having increased at 25.5% per year since 2015 [3]. Constant investment and consolidation in CGT contributed to the growth of the CGT market. Therefore, the potential of the CGT market has led many big pharmaceutical companies to add CGT products to their portfolios [3]. Major regulatory agencies are also actively and cooperatively keeping pace. In 2016, the 21st Century Cures Act (Cures Act) was signed into law in the United States in order to help accelerate the development of CGT products and distribute them to the market faster and more efficiently [4]. Like the U.S., the European Medicines Agency (EMA) has also granted marketing authorization under exceptional circumstances in those extreme situations where a disease is rare or a clinical endpoint is difficult to measure [5]. Following this trend, South Korea enacted "The Advanced Regenerative Medicine and Advanced Biopharmaceuticals Safety and Support Act" in 2020, which secures patient safeguards by swiftly commercializing advanced biopharmaceuticals and implementing an entire life cycle safety management system. The focal points of the act were the priority review process, the customized review system, and conditional approval [6]. As a result, the period of time leading up to market entry for advanced biopharmaceuticals is expected to be shortened by up to four years [7].

The clinical development process of CGT clinical trials also follows the conventional process [8]. However, the FDA has implemented expedited programs: Fast Track Designation, Breakthrough Designation, Accelerated Approval, etc. These programs are designed to help ensure therapies for serious conditions are approved and available to patients as soon as it is concluded that the benefits justify their risks, while still preserving the standards for safety and efficacy. For this reason, most CGT products targeting rare diseases or unmet medical needs qualify for these programs. Notably, the Accelerated Approval program allows for the earlier approval of drugs based on surrogate or intermediate endpoints, and while confirmatory studies referring to late-phase clinical trials required to verify clinical benefits are ongoing [9]. Therefore, in the development of CGT products, well-designed early-phase clinical trials are very important to establish the regimen as well as designing the late-phase clinical trials. This can also shorten the development period and ensure efficiency.

CGT products have unique properties that are very different from chemical drugs [10]. Due to these unique properties, it is difficult to apply a pharmacokinetic approach in the same way as it is applied to chemical drugs, so special considerations are needed for pharmacological and safety evaluation [11,12]. For these reasons, the need for CGT early phase clinical trials is emerging. Thus, we reviewed and compared the domestic and international guidelines for the design of early phase clinical trials of CGT and proposed what needs to be supplemented in the guidelines for future revisions.

METHODS

Guidelines for early CGT clinical trials published in the United States (FDA) [13], Europe (EMA) [14], and Japan (Pharmaceuticals and Medical Devices Agency, PMDA) [15] were investigated and compared [16]. The guidelines for the early phase clinical trials of CGT were investigated (FDA) and the contents related to the clinical trial design were extracted (EMA, PMDA) from the guidelines related to CGT. The guidelines of the Ministry of Food and Drug Safety and the FDA were almost the same, thus the results of this paper were described based on FDA guidelines. The guidelines of the PMDA focused on product manufacturing, quality, and nonclinical tests rather than clinical trials, therefore the ability to compare the guidelines was limited.

Details such as the title and scope of the guidelines are presented in **Table 1**. In **Tables 2** and **3**, the main elements of early-phase study design of CGT products, including study population selection, were also examined from the perspective of comparing those in guidance for design of early-phase clinical trials of small molecules published by the FDA [17-25]. In these tables, the contents of the guidelines were cited as much as possible from the original sentences in order to convey the meaning well. According to the description in the CGT guidelines, previous natural killer (NK) cell phase 1 trials were explored as application examples.

RESULTS

The objective and consideration for early-phase clinical trials of CGT products

In all of the guidelines investigated, the objectives of early-phase trials for CGT products were safety evaluation, preliminary evidence of effectiveness gathering, and determination of dose range as in those for chemical drugs and biologics. In addition, the FDA recommended that feasibility and activity assessments should be included as objectives in trials because of factors such as pretreatment intervention and the manufacturing and administration processes. To evaluate the safety of CGT products, specific dose regimens and routes of administration, upstream interventions on subjects, administration procedures and targeting specific issues (e.g. delayed infusion reactions, autoimmunity, graft failure, graft versus host disease, new malignancies, transmission of infectious agents from a donor, and viral

Table 1. The latest relevant guidelines on design of early phase clinical trials of CGT products

Regulatory agency	Relevant guideline	Year	Published by	Name of products	Explanation
MFDS, South Korea	Guideline on the Design of Early-Phase Clinical Trials of Cell Therapy and Gene Therapy Products [16]	2015	Biopharmaceuticals and Herbal Medicines Evaluation Department	CGT Products	Cellular therapy products, human gene therapy products, and certain devices related to cell and gene therapy (cellular immunotherapies, cancer vaccines, and other types of both autologous and allogeneic cells)
FDA, United States	Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products [13]	2015	Center for Biologics Evaluation and Research (CBER)	CGT Products	Cellular therapy products, human gene therapy products, and certain devices related to cell and gene therapy (cellular immunotherapies, cancer vaccines, and other types of both autologous and allogeneic cells)
EMA, Europe	Guideline on Good Clinical Practice specific to Advanced Therapy Medicinal Product [14], (2. Clinical Trials)	2019	European Commission and EMA	ATMPs	Medicines for human use that are based on genes, tissues or cells (gene therapy medicines, somatic-cell therapy medicines, tissue-engineered medicines)
PMDA, Japan	Ensuring Quality and Safety of Products for Genetic Therapy [15], (Chapter 5)	2019	Pharmaceutical Safety and Environmental Health Bureau	遺伝子治療用医薬品 (Gene Therapy Drugs)	*In vivo* gene therapy products and *ex vivo* genetically modified human cell therapy products (*ex vivo* gene therapy products), among regenerative medical products

ATMP, Advanced Therapy Medicinal Product; CGT, Cellular and Gene Therapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; MFDS, Ministry of Food and Drug Safety; PMDA, Pharmaceuticals and Medical Devices Agency.

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Table 2. Objective and consideration for early-phase clinical trials of CGT products in different national guidelines compared to first-in-human study of small molecule design guidance

Contents	First in human study of small molecule and biological drug (FDA) [17-25]	FDA [13]	EMA [14]	PMDA [15]
Objectives	· To determine the metabolism and pharmacologic actions of an investigational drug in humans · To determine the side effects associated with increasing doses · To gain early evidence of effectiveness	· Safety evaluation · Preliminary evidence of effectiveness gathering · Dose exploration · Feasibility assessment · Activity assessment	· Safety evaluation · To define the dose range to be used in the pivotal trial	· Safety evaluation
Considerations for safety evaluation	· Natural and frequency of potential adverse reactions · Estimation of the relationship to dose	Especially for CGT, · Safety of specific dose regimens and routes of administration · Feasibility of administration and pharmacologic activity · Estimation of the relationship to dose · Evaluations may include assessments targeting specific safety issues that could be anticipated with CGT products. (delayed infusion reactions, autoimmunity, graft failure, GvHD, new malignancies, transmission of infectious agents from a donor, and viral reactivation) · Long-term follow-up	Especially for CGT, · Upstream interventions on subjects and administration procedures · Product administration process, product failure, medical devices, mandatory concomitant medication(immunosuppression) · Long-term follow-up	Especially for CGT, · The possible effects of pretreatment on subjects and safety profile · Unexpected immune responses · Long-term follow-up
Monitoring and follow-up	· Follow up should be long enough to preclude the possibility of undetected serious toxicity	· One year or more of follow-up is appropriate for each subject in early-phase trials.	· Need for patients to be on long-term follow-up after treatment · Adverse events possibly due to unexpected reactions such as hypersensitivity, immunological, toxic; or migration of cells from the target site and ectopic tissue formation	· Set an appropriate period for the follow-up period based on the type of gene therapy drugs · Chromosomal implantation vectors should be observed at least once
Considerations for patient-specific products or CGT products	-	· The product needs to be manufactured separately for each subject in a trial. · Manufacturing of some CGT products may take many weeks or months. Thus, the trial might include separate criteria that need to be met at the time of product administration. · Problem in product manufacturing can facilitate design of subsequent trials by suggesting subject selection criteria to reduce the chance of failure, or by prompting the development of a treatment protocol with a formalized manufacturing failure contingency plan. · Due to failure to administer the CGT product to a subject, the protocol should also clearly specify whether re-treatment will be attempted with another round of manufacturing and whether an untreated subject will be replaced by increasing enrollment. · Failure-to-treat may be an important trial endpoint that is part of a feasibility evaluation.	· Risk-minimization measures (e.g. if the results of the sterility test of the product are not available at release, appropriate mitigation measures should be described. Or if there is a risk that a subject that has received an investigational ATMP develops cytokine release syndrome, the investigator should be informed about measures that should be in place before treating the patient.) · Upstream interventions on subjects: In an autologous setting, the process of taking biopsies/ extracting cells may entail risks to the subject and may also have an impact on the quality and safety of the product. · Administration procedure: When the administration process deviates from standard clinical practice, the detailed instructions for administration should be described in the Protocol or IB.	· The effect and safety of pre-treatment on subjects should be clarified in the case of special pre-treatment

(continued to the next page)

Table 2. (Continued) Objective and consideration for early-phase clinical trials of CGT products in different national guidelines compared to first-in-human study of small molecule design guidance

Contents	First in human study of small molecule and biological drug (FDA) [17-25]	FDA [13]	EMA [14]	PMDA [15]
Study population				
Principle of study population selection	· Acceptable balance between the anticipated risks and potential benefits for the subjects	· Acceptable balance between the anticipated risks and potential benefits for the subjects · Ability to detect product's activity, either adverse or beneficial · For most CGT trials, the benefit-risk profile is not acceptable for healthy volunteers.	· The relation of the anticipated benefits to the potential risks of the ATMP should be at least as favorable as existing alternative approaches. · Ability to provide interpretable data	-
Disease stage of severity	· The patient population should be limited to patients with serious diseases for which no curative therapies are available.	· The study population should be chosen with consideration of the potential interpretability of study outcomes. · While severely affected subjects are often included in early-phase CGT trials, they should not be an automatic choice.	· In particular in cases of life-threatening diseases where there is a risk that the trial subjects may not survive until the administration of the investigational medicinal product (e.g. long period required for manufacturing, patient in too critical condition to survive leukapheresis or preconditioning regime).	-
Pediatric subjects	· Expansion cohorts evaluating pediatric populations should be strongly considered if the drug has potential relevance for the treatment. · Sponsors should enroll pediatric patients in dose-finding and activity estimating cohorts after a reasonably safe dose and preliminary activity have been established in adults. · When the data in adults are in available, sponsors should consider staged enrollment of older children or adolescents before younger children.	· Additional safeguards implementation should be considered. · Usually obtain initial safety and tolerability data in adults · In some situation (genetic disease), prior adult studies are unethical or infeasible	· For pediatric subjects or fetuses, additional safeguards implementation should be considered. · Prior studies in adults are performed if possible.	-

ATMP, Advanced Therapy Medicinal Product; CGT, Cellular and Gene Therapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency; GvHD, graft versus host disease.

reactivation) should be considered. All of the guidelines recommended long-term follow-up. In the guidelines by the FDA, the follow-up period was described as one year or more of follow-up being appropriate for each subject in early-phase trials (**Table 2**).

The FDA guidance recommended considering the problems in product manufacturing and failures in administration as subjects for design of clinical trials because CGT products are manufactured separately for each subject in a trial and are then administered to a subject after many weeks or months of manufacturing. The EMA guidance recommended considering the risk and measure of upstream interventions on subjects because the process of taking biopsies/extracting cells may have an impact on not only the subject's safety but also the quality and safety of the product (**Table 2**).

Considerations for choosing a study population of early-phase clinical trials for CGT products

All guidance was based on the balance between the anticipated risks and potential benefits for the subjects and the ability to provide interpretable data or detect a product's adverse or beneficial activity (**Table 2**). From this perspective, the FDA indicated that healthy volunteers are not acceptable for most CGT trials except when the clinical trials are for a product with short duration of action or in a class with a well-understood safety profile.

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Table 3. Recommendations for design of early-phase clinical trials in different national guidelines compared to first-in-human study of small molecule design guidance

Contents	First in human study of small molecule and biological drug (FDA) [17-25]	FDA [13]	EMA [14]
Control group/ blinding	· Purpose: to allow discrimination of patient outcomes caused by test treatment form outcomes caused by other factors · Types: placebo/no treatment/different dose or regimen of the study treatment/a different active treatment · Blinding is usually used minimize the chance of bias · Often double-blind (or double-masked)	· A concurrent control group and blinding are generally not as critical as for a confirmatory efficacy trial. · For some CGT products, use of an intra-subject control may be a useful and convenient way to control a trial. · Standard-of-care and no-treatment controls allow evaluation of the risk of the overall investigational treatment.	· Placebo: The use of placebo should be scientifically and ethically justified. · Comparator: If an active comparator is not available, comparison with best standard of care can be considered. An intra-subject control may also be considered when appropriately justified. · Blinding for subjects should be maintain where possible.
Cohort size	· Justification of sample size chosen to detect clinically important differences in safety and activity, if present · Placebo-controlled studies with eight to ten subjects per cohort randomized in a 3:1 or 4:1 ratio · Standardized protocol designs, such as the 3 + 3 design, are often used for dose escalation of oncology products.	· For CGT products, manufacturing capacity is often limited, which might place a practical limit on cohort size, particularly early in clinical development. The prevalence of the proposed study population may also limit the cohort size. · Standardized protocol designs, such as the 3 + 3 design, are often used for dose escalation of oncology products.	· The cohort size number usually depends on disease prevalence and manufacturing capacity
Staggering administration	· Often adopt during early phases of SAD trials.	· The choice of staggering interval should consider the time course of acute and subacute adverse events.	· Staggered treatment of individual subjects within each new cohort and between cohorts should be considered
Dose and regimen	· Starting dose selection based on NOAEL or MABEL	· It may be difficult to establish an initial starting dose based on the considerations used for small-molecule drugs. · If available, previous clinical experience with the CGT product or related products, even if by a different route of administration or for a different condition, might help to justify the clinical starting dose.	· A rationale for a dose definition based on published literature data requires a thorough analysis of the comparability between products, including on aspects relating to starting material and manufacturing process, as well as the characteristics of patient populations treated.
	· Escalate or de-escalate according to pre-specified rules based on the observed target events (DLT).	· Clinical development of CGT products has often included dose escalation in half-log (approximately three-fold) increments. · The dosing increments used for dose escalation should consider preclinical and any available clinical data regarding the risks and activity associated with changes in dose.	· A dose escalation strategy may not be necessary (e.g. if there are no toxicity concerns associated with the investigational ATMP) or appropriate (e.g. when it is not possible to re-administer the product or when the re-administration involves the additional risk of a surgical procedure).
	· SAD and multiple ascending dose	· Most first-in-human CGT trials use a single administration or one-time dosing regimen. · However, some CGT products, such as therapeutic vaccines may use multiple administrations.	· Aspects of dosing and repeatability of treatment should be duly considered based on the specific characteristics of the product. · For example, where the ATMP is expected to have long-term effects, dose escalation and repeated dosing should be considered with a view to improve the control of toxicity risks to the subject.
	· Stopping dosing of study drug in an individual subject or for stopping a study altogether.	· Collecting data on various cell subsets in the final CGT product in situation where there is uncertainty about the cell subset(s) responsible for the therapeutic or adverse effect. · For many GT products, dose is based on vector titer. · For gene-modified cells, dosing should consider several factors, including transduction efficiency (in addition, the total number of cells administered to subjects, the mean number of copies of vector sequences integrated per cell, and cell viability).	-

ATMP, Advanced Therapy Medicinal Product; CGT, Cellular and Gene Therapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; MABEL, minimum anticipated biologic effect level; NOAEL, no observed adverse effect level; SAD; single ascending dose.

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For early-phase clinical trials of small molecules, the patient population should be limited to patients with serious diseases for which no curative therapies are available. On the other hand, severely affected subjects should not be an automatic choice for early-phase CGT trials because the trial subjects may not survive until the administration can occur after the long period required for manufacturing. Also, the disease's stage of severity should not cause difficulties in data interpretation. The PMDA recommended specifically designated patients with a life-threatening disease such as cancer for a study population.

For pediatric subjects in early-phase trials of small molecules, an expansion cohort to enroll pediatric subjects should be strongly considered based on safety and potential relevance data from prior clinical trials in adults. Clinical trials in pediatric subjects can be conducted with the implementation of additional safeguards, and pediatric trials for specific CGT products (e.g. genetic disease) can be carried out without prior studies in adults (**Table 2**).

Consideration for design of early-phase clinical trials

A control group purposes to distinguish patient outcomes caused by test treatment from outcomes by other factors. Blinding can help by minimizing the possibility of bias (**Table 3**). The early-phase clinical trial of CGT products does not necessarily need a control group and blinding given its purposes. As a control group, factors such as standard-of-care, no treatment, and if possible, intra-subject control may be useful.

The sample size is estimated to detect the clinically significant differences in efficacy and safety. In early-phase clinical trials, placebo-controlled studies have 8–10 subjects per cohort, in which subjects are randomized in a 3:1 or 4:1 ratio. Many early-phase trials of oncology products often used standardized protocol designs, such as the 3+3 design. This can be also applied to the design of CGT early-phase trials. Their cohort size number may be limited by disease prevalence and manufacturing capacity (**Table 3**).

To define the dose range to be used in the later phase is one of the objectives in an early-phase clinical trial of small molecules and biologics [24,25]. Thus, there are robust approaches as follows: No Observed Adverse Effect Level or Minimum Anticipated Biological Effect Level for starting dose selection and dose escalation procedures based on dose-limiting toxicity, etc. (**Table 3**). These approaches may be difficult to apply to a selection of an initial dosing for CGT products, therefore it can be established based on previous clinical experience or published literature analysis. The FDA guidance describes CGT trials in the early-phase have often included dose escalation in half-log (approximately three-fold) increments while the EMA describes that a dose escalation strategy may not be necessary or appropriate. In addition, most first-in-human CGT trials use a single administration or one-time dosing regimen. If the CGT product is expected to have long-term effects, the EMA recommended that dose escalation and repeated dosing should be considered to the extent that it is possible to manage toxicity to the subject.

Case analysis: early-phase clinical trials of autologous NK cell therapy

In order to explore the actual design of the early-phase clinical trial of CGT products, previous literature of early-phase trials for the autologous NK cell were analyzed [26-29]. The design, biomarkers, and results of those phase 1 trials were summarized in **Table 4**. The study population in these studies were patients with various types of advanced cancer including lymphoma, non-small cell lung cancer, and gastric cancer. The sample size was a small, ranging from 10–30 subjects. The dose of NK cells used in those trials was in the range of 1–6 × 10^9 cells per injection, however the interval and frequency of administration differed from study

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Table 4. The comparison of phase 1 clinical trial design for autologous NK cell therapy

References	Subjects & sample size	Dose & regimen	Sampling point to measure biomarkers	Biomarker	Results of biomarker analysis
Olioso et al. [26]	Refractory/relapsing lymphoma or metastatic solid tumors (n = 12)	· NK cell therapy alone · Dose: 28 × 10^9 (6–61) cells/injection · Every 3 weeks for 3 cycles	· Baseline before each treatment · Day 1 after each administration · Day 7after each administration	· NK cell population · Cytotoxic assay · Immunophenotypic & cytokines analysis in patients' peripheral blood	· Absolute median count of lymphocytes, CD3+, CD8+ and CD3+CD56+, IFN-γ, TNF-α cells significantly increased.
Sakamoto et al. [27]	Unresectable, locally advanced and/or metastatic digestive cancer (n = 14)	· NK cell therapy alone · Dose: 0.5 × 10^9, 1.0 × 10^9, and 2.0 × 10^9 cells/injection · Every week for 3 cycles · Dose escalation with 2 fold increments	· Baseline (day 0) · Before the 3rd administration (day 14) · 4 weeks after 3rd administration (day 42)	· NK cell population · Cytotoxic activity · Serum cytokine assay	· NK cell population in peripheral blood lymphocytes slightly increased until day 42. · Cytokine serum levels did not change significantly.
Yu et al. [28]	Stage III-IV non-small cell lung cancer (n = 30)	· Chemotherapy and NK cell therapy · Between 2 × 10^9 and 6 × 10^9 cells/injection · Once a day for 3 consecutive days	· Baseline · 2 weeks after administration · 4 weeks after administration	· PBMC phenotype · NK cell population · Plasma cytokine · Chemokine assay · Cytotoxic assay	· The percentage of NK cells, NKG2D expression, cytokine significantly increased by week 2
Ishikawa et al. [29]	Advanced gastric or colorectal cancers (n = 9)	· Trastuzumab- or cetuximab-based chemotherapy, plus NK cell therapy · Dose: 0.5 × 10^9, 1.0 × 10^9, and 2.0 × 10^9 cells/injection · Every 3 weeks for 3 cycles · Dose escalation with a sequential 3 + 3 design	· Baseline, 7 days after 1st administration · 7 days after 3rd administration · 28 days after 3rdadministration	· NK cell population · Multiplex cytokine assay	· Levels of IFN-γ and IL-2 were significantly increased at 7 days after first administration.

IL-2, interleukin-2; IFN-γ, interferon-gamma; NK, natural killer; TNF-α, tumor necrosis factor-alpha; PBMC, peripheral blood mononuclear cell.

to study. The rationale of dose selection and regimen were not stated in the articles. To explore biomarkers to evaluate safety or activity of autologous NK cells, levels of NK cell, T cell, and cytokines in the blood were measured before and after treatment in all studies, however the timing of blood collection was set differently for each study. The results of the biomarkers showed clinically significant changes, however, there was a limitation to ensure valid data about the activity of autologous NK cells due to the differences in dose range and regimen.

Although all of the studies were conducted before 2015, when the guidelines were released, the designs of all of the studies were consistent with the guidelines. The primary purpose of the studies was safety evaluation. In addition, early evidence of effectiveness and safety was obtained by measuring biomarkers. Inclusion/exclusion criteria were established so that study population should be limited to patients with serious diseases for which no curative therapies are available, excluding patients with immune disorders to provide interpretable data for safety evaluation. The sample size was set to the minimum number capable of detecting safety and activity of the investigational products. On the other hand, all of the studies used multiple administrations and conducted safety evaluations up to 28 days after the last administration. This seems to be because there was a basis for the empirical use of autologous NK cells and it was considered relatively safe [30]. It is presumed that the differences in dose and regimen between each study stemmed from the differences in the conditions of the donor and non-clinical data that were the basis for their setting. Based on previous findings, subsequent autologous NK cells' studies have been designed with administrations every 3 weeks with more than 3 cycles within the reported dose range [31-33].

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DISCUSSION

In the development of CGT products, the early-phase clinical trials are important because there are limitations in obtaining relevant information from the non-clinical studies and how clinical trials are conducted in numbers of subjects. Thus, the regulatory agencies have provided guidelines to support early-phase clinical trials for CGT products which have been growing rapidly. These guidelines described the safety evaluation, preliminary evidence of effectiveness, dose exploration, and feasibility assessments as objectives of early-phase clinical trials for CGT products in common. In addition, the considerations for the design of early-phase CGT products included the pretreatment effect and problems in the manufacturing and administration processes. The guidelines also covered the selection of a study population, control group/blinding, and dose/regimen planning. There were differences in the degree of detail, description, and the scope of the content covered by each guideline. The guidelines published by the FDA were the most specific. However, when compared with the previous guidelines for designing early-phase clinical trials for small molecules and biologics, the current guidelines need to be revised to suggest more detailed and practical principles and rules.

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