Research Plan

1. Title of Research:

Elucidation of the mechanism of peri-operative immunosuppression due to intraoperative anesthetics (propofol, desflurane and sevoflurane) and the effect on the prognosis in patients undergoing lung cancer surgery.

2. Organization of the study

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【Research collaborators】 Practical guidance for experiments, advice on data analysis.

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3. Research protocol and duration

(1) Study period: 2018 approval date to March 31, 2023

(2) Type and design of the study; prospective randomized controlled trial.

(3) Outline of the study

We will conduct a preliminarily study of 10 patients in each group during the first 3 months from starting the study. In this study, CD4/8 ratio and naïve memory ratio will be calculated and compared with the control group to calculate the required number of patients for this study by power calculation.

Study 1) Effect of each anesthetic drug on immunosuppression in lung cancer patients

A) Changes in the number of immune response cells

Peripheral blood samples will be collected from lung cancer patients who undergo the scheduled lung cancer surgery at Juntendo University Hospital before and after surgery.

Peripheral blood mononuclear cells will be isolated from the peripheral blood, and the CD4/CD8 ratio and naïve/memory cell ratio will be calculated using a flow cytometer to evaluate the state of T cell exhaustion.

These parameters will be compared with each anesthetic used in the perioperative period (desflurane, sevoflurane, and propofol).

(4) Summary of the study drug/medical device information

Product name (generic name): ① Supraren (desflurane) ② 1% Diprivan (propofol) ③ Sevofuren (sevoflurane)

Classification, dosage form, standard, etc.: ① 1ml of desflurane in 1ml ② 10mg of propofol in 1ml. ③ 1ml contains 1ml of sevoflurane

Company/Country of manufacture and sale: ① Baxter Corporation (Japan) ② AstraZeneca K.K. (Japan) ③ Maruishi Pharmaceuticals (Japan)

Storage: ①Store at room temperature. ②Store below 25°C to avoid freezing. ③Store at room temperature.

For details, please refer to the attached document.

Anticipated adverse events

In each ① ②and ③, hypotension may occur as a general effect of anesthetics, but it can be treated within the clinical range.

(5) Method of administration of the study drug
Method of administration of the study drug: Same as that used for conventional general anesthesia.

(6) Regulations on concomitant medications (therapy)
①Concomitant use with adrenergic agents may cause tachycardia. Concomitant use with central nervous system depressants enhances the anesthetic effect of desflurane, and concomitant use with muscle relaxants enhances the muscle relaxant effect.
②Concomitant use with benzodiazepines, barbiturates, general anesthetics, local anesthetics, CNS depressants, alcohol, antihypertensive agents, and antiarrhythmic agents (beta-blockers) will mutually enhance the effects (anesthesia, sedation, hypotension, and decongestant).
③ Concomitant use with adrenergic agents may cause arrhythmia, potentiate the effects of nondepolarizing muscle relaxants, potentiate the antihypertensive effects of beta-blockers, alpha2-receptor stimulants, and calcium channel blockers, and potentiate the central nervous system effects of morphine hydrochloride.

(7) Provisions for dose reduction and drug withdrawal; not applicable

(8) Method of case enrollment and allocation: After obtaining the consent form, subjects will be enrolled in three groups. Subjects will be allocated by the permuted block method.

(9) Expected duration of participation in the study; subjects will participate in the study for a 6-month observation period after consent.

(10) Observation and examination items
1) Basic information on the research subject: age, sex, weight, height, name of diagnosis, comorbidities, medical history, electrocardiogram and respiratory function test
2) Anesthesia-related factors (anesthetic dosage, IV fluids, urine volume, anesthesia time)
3) Surgical factors (surgical procedure, surgical time, blood loss)
4)Immunological examination (CD4/CD8 ratio of peripheral blood mononuclear cells isolated from peripheral blood, naive memory cell ratio)

5) Postoperative outcome; postoperative hospitalization period

4. Selection Policy for Research Subjects

(1) Research subjects

Patients undergoing lung cancer surgery at Juntendo University Hospital, Department of Respiratory Surgery will be included in the study.

(2) Selection criteria

①Age 20 years or older at the time of obtaining consent.

②Patients must undergo unilateral surgery.

③ Patients with primary or metastatic lung cancer.

④ Patients who, after receiving sufficient explanation and understanding, freely and voluntarily give written consent to participate in this study.

(3) Exclusion criteria

①Patients taking immunosuppressants or steroids

② Patients who have already undergone chemoradiation therapy

③ Simultaneous bilateral surgery

④ Patients with autoimmune diseases such as collagen diseases

⑤Patients who are judged by the principal investigator to be inappropriate as research subjects

Of the research subjects in (1) above, those who meet all of the selection criteria in (2) and none of the exclusion criteria in (3) will be eligible.

(4) Discontinuation criteria

① When the research subject declines to participate in the research or withdraws consent.

② When this entire research is discontinued.

③ For any other reason, the principal investigator or sub-investigator decides that it is appropriate to discontinue the research

5. Rationale for the scientific rationale of the research

(1) Target number of patients and rationale for setting the target

A preliminarily study will be conducted on 10 cases in each group over a period of 3 months from April 2018. The CD4/8 ratio and naïve memory ratio will be calculated and compared with the control

group to calculate the required number of patients for the study by power calculation (significance level: 0.05, power of test: 0.8).

(2) Statistical analysis method

Statistical analysis methods: Student T test, repeated measures ANOVA, Wilcoxon test, Kruskal-Wallis test will be used in appropriate. For missing values, multiple imputation will be performed.

6.Procedures for obtaining informed consent in accordance with the provisions of the new ethical guidelines (Article 12)

The consent explanation document approved by the hospital ethics committee shall be given to the research subject, and the research subject's free and voluntary consent shall be obtained in writing through sufficient written and oral explanation. In principle, a respiratory surgeon will also be present. When information that may affect the consent of the research subject is obtained, or when changes are made to the research protocol, etc., that may affect the consent of the research subject, information will be promptly provided to the research subject, and the research subject's will as to whether or not to participate in the research will be confirmed beforehand. The consent explanatory document, etc., will be revised with the prior approval of the hospital ethics committee, and the research subject's re-consent will be obtained.

The consent explanatory document shall include the following information

①The name of the research and the fact that permission to conduct the research has been obtained from the head of the research institution (hospital director).

②The name of the research organization and the name of the principal investigator (including the name of the joint research organization and the name of the principal investigator of the joint research organization, if the research is to be conducted jointly with other research organizations).

③ Purpose and significance of the research.

④ Method of the research (including the purpose of use of the samples and information obtained from the research subjects) and duration.

⑤Reason for selection as a research subject

⑥ Burden on the research subject and anticipated risks and benefits.

⑦A statement that the researcher may withdraw consent at any time, even if the researcher has given consent for the research to be conducted or continued.

⑧A statement that the research subjects will not be treated disadvantageously by not consenting or by withdrawing consent.

⑨Method of information disclosure regarding the research.

⑩At the request of the research subject, access to or inspection of the research protocol and materials related to the research methods, to the extent that such access does not interfere with the protection of personal information of other research subjects

⑪Handling of personal information, etc.

⑫Methods of storage and disposal of samples and information.

⑬Situation regarding the source of funding for the research, etc., conflicts of interest pertaining to the research of the research institution, and conflicts of interest pertaining to the research of the researcher, etc., including personal earnings, etc.

⑭Response to consultation, etc., from research subjects, etc., and their related persons

⑮If there is any financial burden or gratuity to the research subjects, etc., a statement to that effect and the details thereof.

⑯ In the case of research involving medical treatment beyond the scope of normal medical care, matters concerning other treatment methods, etc.

⑰ In the case of research involving medical treatment beyond the scope of normal medical care, measures related to the provision of medical care to research subjects after the research is conducted.

⑱If the implementation of the research is likely to result in important findings concerning the health of the research subject, genetic characteristics that may be passed on to offspring, etc., the results of the research pertaining to the research subject shall be handled.

⑲In the case of invasive research, the existence and contents of the compensation for the health damage caused by the research.

⑳If there is a possibility of using the samples and information obtained from the research subjects for future research that is not specified at the time of receiving the consent from the research subjects, etc., or providing them to other research organizations, the possibility and the expected contents at the time of receiving the consent.

㉑In the case of research that involves a surgical invasion (excluding minor invasion) and intervention, on the premise that the confidentiality of the research subjects will be preserved, those engaged in monitoring and auditing and the hospital ethics committee will have access to the samples and information concerning the research subjects to the extent necessary.

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