Towards High-quality Clinical Trials And
Implementation Of Genomic Medicine

ATLAS Training Program

Course : CRC Training Course
Lecture Title : The General Role Of CRCs In Cancer Clinical Trials
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ATLAS
ASIAN CLINICAL TRIALS NETWORK FOR CANCERS PROJECT

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

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■ Education

・1995 JIKEI Nursing School, Tokyo

■ Work Experience

・2021.07 –present : National Cancer Center Hospital (Researcher)

・2009–2021.06 :National Cancer Center Hospital (CRC)

・1995–2008 : Jikei University Hospital (Nurse)

■ Qualification

・Registration of Nurse

・SOCRA CCRP

・JSCTR Oncology Clinical Research Ex pert

Role of CRC* in Cancer Clinical Trials

[The purpose of a clinical study is to generate reliable information for answering research questions and enabling decision making (ICH-E8)]

*CRC：Clinical Research Coordinator

In Europe and the US, this role is referred to as the study coordinator, research nurse, study nurse, etc.

Characteristics of Cancer Clinical Trials

- Serious life-threatening disease
- Safer and more effective treatments are needed
- Cancer clinical trial designs are diversifying and cancer drug development is shifting to based on genetic alterationss
- The tendency of toxicity varies depending on the investigational drug

Elements Required of CRCs in Cancer Clinical Trials

- It is important to always consider the following:

  What is good research?

  What are the demands of the society?

  Why is this be done?

- **CRCs manage the entire clinical trial to ensure that the trial is conducted ethically, scientifically, safely, and properly**

  - CRCs are required to have highly specialized knowledge, skills, experience, and coordinating ability

Main Roles of CRCs in Cancer Clinical Trials

1. Provide support to subjects participating in cancer clinical trials
2. Provide support for conducting cancer clinical trials
    1) Support for scientific assurance
    2) Support for safety assurance
    3) Support for integrity assurance

1. Provide Support to Subjects Participating in Cancer Clinical Trials

Ethics Related to Medical Research

1947Fin	Nuremburg Code Guidelines for protecting the will and freedom of subjects in medical research
1948	Declaration of Geneva Rules on medical ethics
1964	Declaration of Helsinki Ethical principles for medical research on human subjects It is recommended that people involved in medical research other than physicians also adopt these principles
1979	**Belmont Report** Principles for the protection of human subjects

Belmont Report

Respect for persons: Obtain consent based on free will

Is the autonomy of the individual respected and is protection of personal information promised?

Beneficence: Risk and benefits of the entire research plan

Is the plan comparable with the current best methods and treatments?

Justice: The research is administered fairly

Is the distribution of benefit and burden fair, and is the selection of participants fair?

Proper measures for persons who require special social consideration

Where are research ethics found in the protocol?

Research background : Academic significance
(Medical) development from previous research

Purpose : Social value
The study results are expected to contribute to future medical care

Methods : Scientific validity (possibility of implementing research)

Validity of the study population (validity of eligibility criteria)

Providing support to subjects participating in Cancer Clinical Trials (1)

- **Participants in cancer clinical trials are “Cancer Patients” (not healthy volunteers), because aanticancer drugs are more toxic than other drugs and may affect healthy cells.**

CRCs must be skilled in collecting and sharing the information to adapt to the complex background of cancer patients participating in clinical;

- Patients have various symptoms caused by the primary disease and associated complications
- Need to properly evaluation a large number of inclusion and exclusion criteria
- Need careful patient observation to determine whether adverse events are due to cancer symptoms or investigational product
- Correctly reports the subject information obtained to PI, and appropriate support of adverse event assessment by PI.
- Judgement of necessity of psychological care for subjects at the time of study treatment discontinuation

Communication Skills

Basic Communication Skills Required By Health Professionals

Preparation Affects how the other person's message is received and interpersonal relationships	・Be dressed for the occasion, greet the person, be well-mannered, be punctual, and ask permission to answer the phone
Listening skills Reiterating the patient's comments leads to a mutual understanding of the message being conveyed and awareness of deviations in the conversion code	・Watch the other person's eyes and face, maintain the line of sight at the same height, encourage the other person to talk by not interrupting, and repeat what the other person says in your own words
Questioning skills The ability to show interest in the other person's life and values and not just in the clinical trial	・Use open-ended questions that require more than a yes/no answer and use easy-to-understand words
Responding skills Can improve the other person's satisfaction with the communication	・Seek out and understand what is being said by the other person, rephrase the other person's words to convey that you understand the meaning, and provide fact-based information
Empathy skills Serves as a facilitator who responds to problems and issues	Accept the person's feelings, explore his/her feelings, and clearly convey that these feelings are understandable

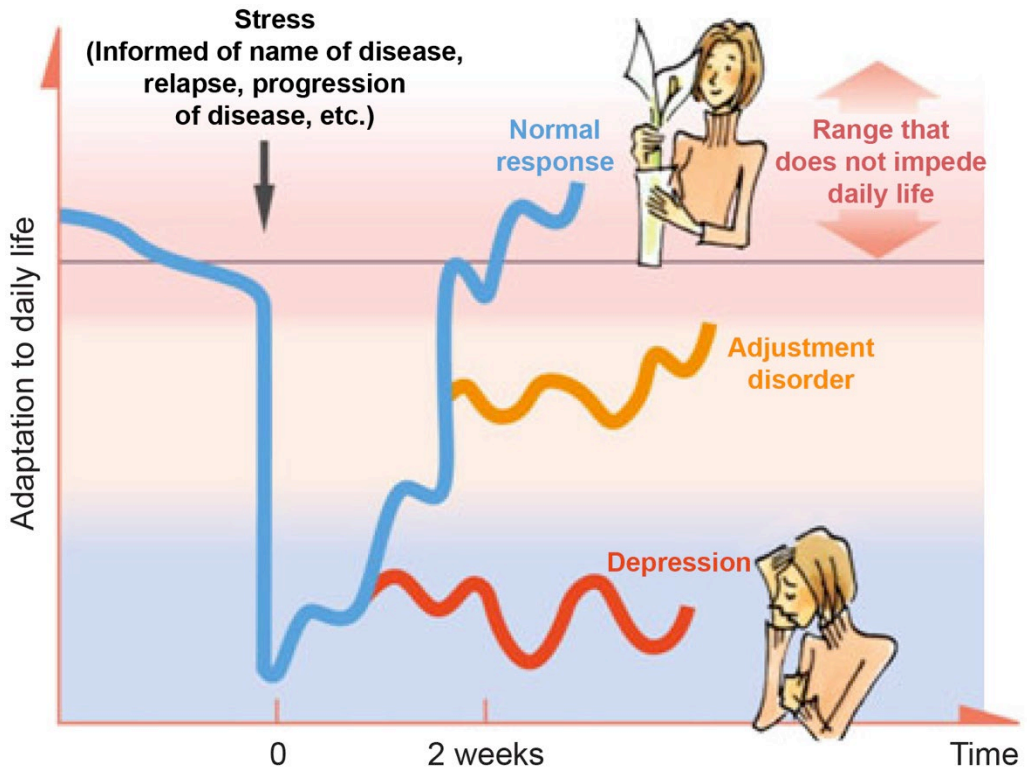
Psychological Processes Experienced By Patients With Cancer

	Feelings/Response		Symptoms
Stage 1 Shock and denial, despair	Did I do something wrong? Is this a mistake? I can't possibly have cancer!	・Doesn't feel real ・Unable to concentrate	・Emotional paralysis ・Constantly worrying ・Irritated ・Unable to enjoy life ・Unable to sleep ・No appetite ・Listless, tire easily
Stage 2 Depression	Why do I have to suffer like this?	・Anger ・Alienation ・Anxiety, depression	
Stage 3 Adaptation	It can't be helped that I have cancer; I will do what I can!	(・Readaptation, recovery)	Start realistic processing of the situation, such as gathering information and organizing work

Psychological Support For Subjects

- Emotional support
  - Empathic attitude, consideration, listening
- Provide information at an appropriate time
  - Treatment (disease, standard treatment, clinical trials)
- Medical support for psychiatric symptoms
  - Psychiatric oncology intervention

→ Additionally, as a medical professional, one must consider “evaluating the problem” and “solving the problem” while listening to the patient



Cited from: Cancer Information Service_Cancer and the Mind, National Cancer Center Hospital

Providing support to subjects participating in Cancer Clinical Trials (2)

- Patients with a disease that causes physical and psychological distress characterized by anxiety and pain after being diagnosed with cancer

Observation and care of social and psychological conditions
Ensure that the patient is not under the misapprehension that the trial is the treatment (“therapeutic misconception”)

- Only recently notified (diagnosed) of the cancer
- Immediately after ineffective treatment or confirmation of progression
- Constantly anxious about treatment and death

2. Support for conducting Cancer Clinical Trials

Support for conducting Cancer Clinical Trials

- Cancer Clinical trials for multidrug therapies and multidisciplinary therapies are required to establish a standard treatment
- Complex protocol rules

  Pre-treatment requirements (treatment regimens and number of regimens), administration criteria, and Dose modification c riteria (suspension/dose reduction etc.)
- The frequency and severity of adverse events is often high

Understand the latest standard cancer treatments and protocol treatments

- Basic knowledge of cancer pharmacotherapy, i.e. standard treatment for each organ
- Expected adverse events (timing and severity of occurrence) and treatment for the investigational product

Support for scientific assurance

Selecting suitable subjects (1)

- Is the subject eligible?
  - Does the subject meet the inclusion/exclusion criteria; is the person vulnerable?

Inclusion criteria : Assume patients who would receive treatment in the future

Criteria used to define a patient group for whom the treatment would be considered valid if the clinical research is shown to be effective

Exclusion criteria : Prevent disadvantage for the subject

Criteria that stipulates that under certain circumstances the risk to the subject is too high and participation is unethical, and it is determined that it will affect the evaluation of the efficacy and safety of the clinical research

Socially vulnerable people : Prevent improper treatment and secondary damage to subjects

The “socially vulnerable people” group includes individual subjects or groups of subjects with limited autonomy due to disability, illness, age or other (social) circumstances; it includes students or hospital staff who would find it difficult to refuse a request from healthcare professionals

Support for scientific assurance

Selecting suitable subjects (2)

- Check pre-treatment history
  - When is ● day after pre-treatment? (continuous administration, combined injection, and oral therapy)
- Use of drugs contraindicated for coadministration
  - Whether the patient is taking or wishes to take non-prescription supplements or health foods
- Whether the patient can comply with the protocol schedule

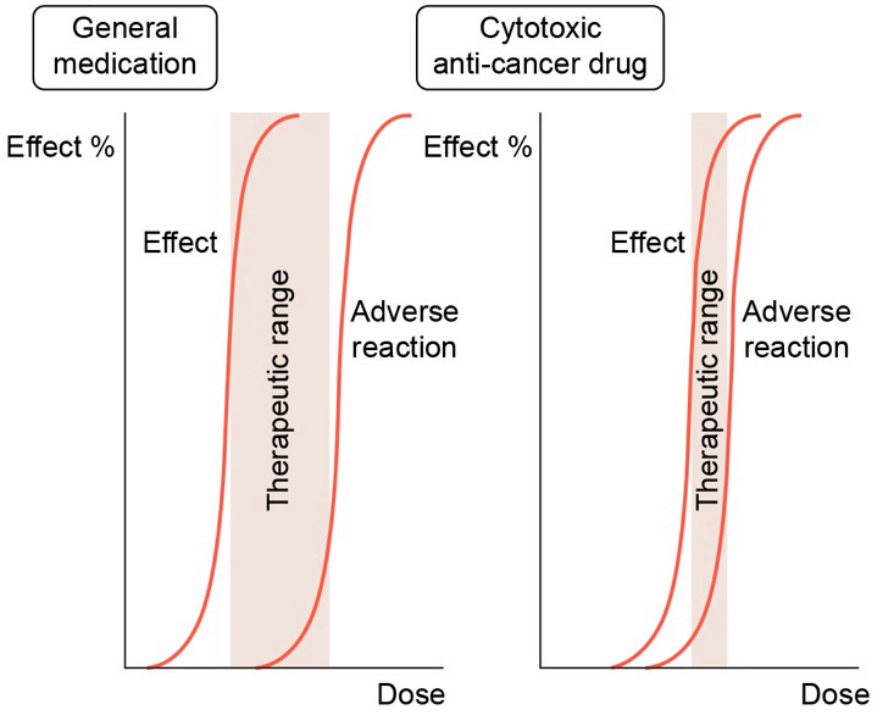
Support for scientific assurance

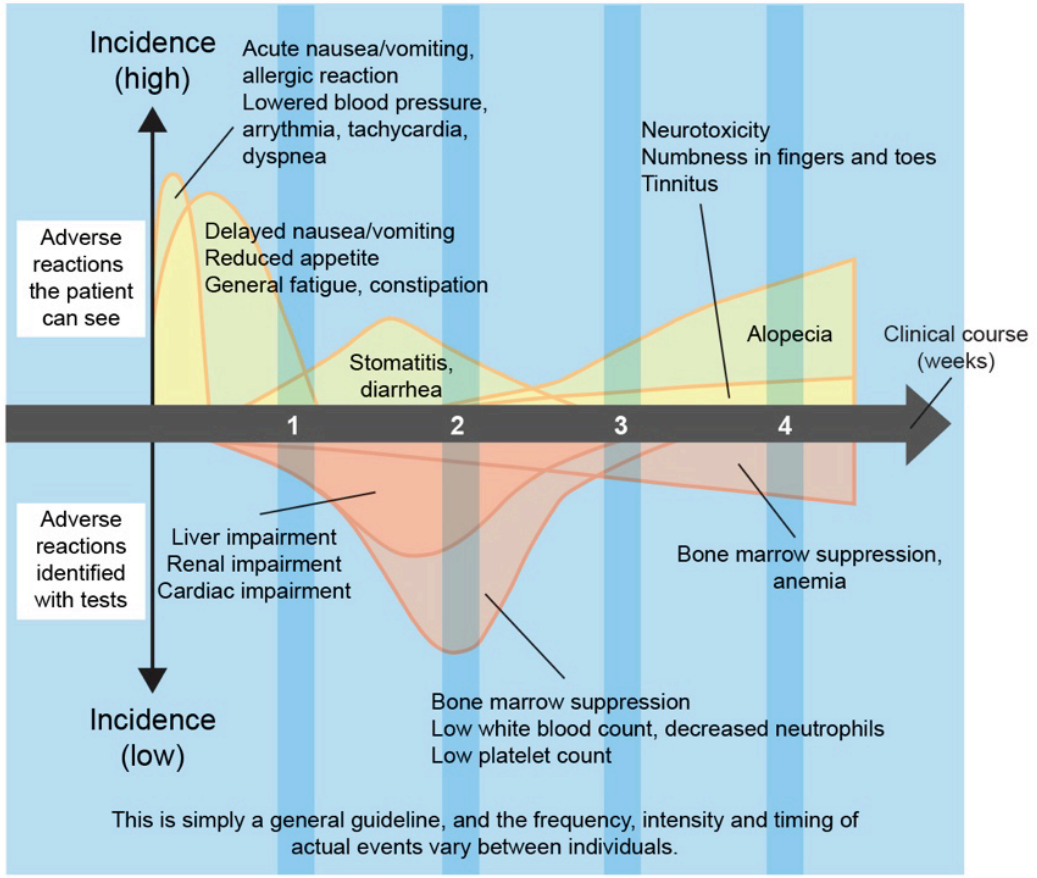
Understanding evaluation criteria

- **Efficacy** endpoints
  - Tumor shrinkage effect
  - Response Evaluation Criteria in Solid Tumors (RECIST)
- **Time to event** endpoints
  - Overall Survival (OS), Progression-free Survival (PFS), Disease-free Survival (DFS)
- **Safety** endpoints
  - Onset of adverse events
  - NCI Common Terminology Criteria for Adverse Event (CTCAE)

Support for safety assurance

Characteristics of drugs used in Cancer Clinical Trials (1)





Cytotoxic anti-cancer drugs adverse reactions and onset timing

Support for safety assurance

Characteristics of drugs used in Cancer Clinical Trials (2)

Type	Main cancers	Adverse reactions
EGFR inhibitors (EGFR/KRAS mutation)	Non-small cell lung cancer Colon/rectal cancer, etc.	Skin disorders, diarrhea, gastrointestinal bleeding, drug-induced pneumonia
ALK inhibitors (ALK-fusion gene)	Non-small cell lung cancer	Nausea, vomiting, diarrhea, constipation, visual abnormalities
HER2 inhibitors (HER2 overexpression)	Breast cancer Stomach cancer, etc.	Cardiac function impairment, infusion reaction (fever, reduced blood pressure, etc.)
Angiogenesis inhibitors Multikinase inhibitors	Colon/rectal cancer, breast cancer, ovarian cancer, renal cell carcinoma, gastrointestinal stromal tumor, hepatocellular carcinoma, etc.	Bleeding from the mucous membrane, hypertension, proteinuria, hand-foot syndrome
Immune checkpoint inhibitors	Malignant melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, head and neck cancer, malignant pleural mesothelioma, stomach cancer, esophageal cancer, MSH-high colon/rectal cancer, etc.	Immune-related adverse event：irAE interstitial lung injury, colitis, intestinal perforation, encephalitis, Guillain-Barré syndrome, acute adrenal failure, fulminant type 1 diabetes, myocarditis, severe skin disorders

Support for safety assurance

Responding to Adverse Events

Anti-cancer drugs have a narrow therapeutic range, and adverse reactions always occur!

- Correctly identifying the patient's symptoms
  - Personality? Cancer symptoms? Adverse reactions?
- Collect information regarding the adverse events from the IB* and previous phase studies, and understand the drug characteristics
- SAE** are common

Clinical trials investigating immunotherapy and molecular targeted therapy etc., have become commonplace in recent years…

- Initial symptoms of irAEs are not consistent, but are diverse
- AEs may become serious and even fatal within a matter of days

IB*: Investigator's brochure
SAE**: Serious adverse event

Support for Integrity Assurance

Data integrity

- Conduct the reserch in compliance with protocol
- Behaviors that undermine integrity include；
  - Fraudulent behavior (fraud)

    The research is completely discredited because of malicious acts that intentionally skew the facts
  - Misconduct

    Possibility of systemically distort the clinical trial conclusions
  - Inadvertent errors (errors/honest errors)

    Non-malicious, unintentional error; almost impossible to completely eliminate these errors…

Support fr Integrity Assurance

Data integrity

Errors/Honest Errors In Clinical Trials	
Data errors	Almost found in source data or EDC
Deviations from the protocol/manuals.	Records are not always kept. In some cases, the details process are not captured in the medical chart or EDC.
Ineligible/incorrect registration	The processes is usually recorded in medical chart / EDC and is easily found.
Loss of study documents/ Incorrect descriptions in document	All study documents including source data are applicable. Although these errors can be easily found, they can also be adjusted by creating replacements or follow-up documents, which tends to result in misconduct

* To create appropriate records (quality assurance of source data), information related to the clinical trials is recorded in conformance with ALCOA-CCEA.
* It is important to establishment the system for minimizing errors that affect subject safety (QMS activities).

Support for Integrity Assurance

Source data records: ALCOA-CCEA

Cannot confirm any study processes from source data records = Decline of reproducibility and integrity

1. Follow the clinical course of the subject

   Record without delay (on the spot)

2. Records must explain the facts, results, and determination

   Clarify not only the results, but also the process and reason for any corrections or changes

Role of CRC in Cancer Clinical Trials -In Summary-

- After receiving a diagnosis of cancer, with bad news of disease progression
  - Participation of clinical trials will be a treatment
- Once the purpose and risk-benefit of the study is understood…
  - Subjects themselves **can make the convincing choices** throughout the clinical trial participation
- Multidisciplinary collaboration is essential to conduct clinical trials appropriately and reach goals while ensuring the scientific and safety of the trial

Main duties of CRC in Cancer Clinical Trials

Fully understanding of complex protocol

Ability to manage the trial to ensure that it is properly conducted in accordance with the protocol

Source data record and storage (ALCOA)

Collecting and monitoring the latest safety information

Knowledge of adverse events and proper evaluation of efficacy (CTCAE/RECIST)

Prompt and appropriate response for SAEs

Psychological support for the patient and patient's family

Communication skills with end-of-life patients

Cooperation with other medical professions

Cooperation with the study sponsor

References and Citation

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