Chapter 6

Slide1

Last, I will explain about the identification of genetic abnormalities in normal cells that are associated with serious adverse reactions to anticancer agents. I will explain how this information is used to determine whether or not an anticancer agent is administered and the dose.

The gene abnormalities in question are UGT1A1 polymorphisms.

Slide 2-3

Let us review the term gene polymorphism.

Roughly speaking, the gene abnormalities I have talked about thus far are extremely rare changes (i.e. a frequency of less than 1 in 100 people). These genetic changes harm the body, like an EGFR mutation that causes lung cancer and BRCA1 that causes breast cancer and ovarian cancer.

In contrast, a gene polymorphism is noted at a considerable frequency since it occurs in more than 1 in 100 people. This genetic change will pose no problems in terms of normal life. Although some gene polymorphisms will have absolutely no effect on the survival and evolution of humanity, some unexpectedly might affect the survival and evolution of humanity. In an easily explainable example, some people can tolerate alcohol while others cannot. Gene polymorphisms are one factor that determines a person's tolerance. Polymorphism in a gene coding for an enzyme that breaks down alcohol causes diminished enzyme activity in some people, making them less able to tolerate alcohol. Alcohol is consumed and turns into a toxin known as acetaldehyde in the body. Acetaldehyde is converted into acetic acid by an enzyme known as ALDH in the liver, where acetic acid is then broken down into water and carbon dioxide.

If, however, there is a polymorphism in the gene for the enzyme ALDH, then acetaldehyde cannot be converted into acetic acid. ALDH will accumulate in the body, causing a person to immediately become drunk and suffer a hungover later.

However, this genetic change poses no problem to the survival and evolution of humanity whatsoever if people do not consume alcohol.

When a polymorphism occurs in an enzyme that breaks down an anticancer agent, it can cause a more severe adverse reaction to occur.

Slide 4

That anticancer agent is irinotecan.

Irinotecan is a semisynthetic derivative of an anticancer drug called camptothecin that is extracted from the fruit and roots of a tree known as the Happy Tree or Cancer Tree (Camptotheca acuminata

Decne).

When irinotecan is hydrolyzed, its active form is known as SN-38. Irinotecan exhibits antitumor action by inhibiting topoisomerase 1.

Irinotecan is approved for the treatment of numerous types of cancer, including small cell lung cancer, non-small cell lung cancer, cervical cancer, ovarian cancer, gastric cancer, colon cancer, and breast cancer.

Slide 5

Irinotecan is infused intravenously. Carboxylesterase in the liver converts it into its active form, SN-38, as I mentioned a moment ago. SN-38 had anticancer action, but it can also cause adverse reactions.

In the body, SN-38 is inactivated and detoxified by UDP-glucuronosyl transferases (UGTs).

The UGT1A1 gene codes for a UGT that is involved in that detoxification. A certain percentage of people are born with a polymorphism in that gene. If people with the polymorphism develop cancer and they receive irinotecan, it cannot be fully detoxified and they will suffer severe adverse reactions.

Slide 6

Patients with the polymorphism *28 or *6 in UGT1A1 have a high risk of serious adverse reaction to irinotecan.

In specific terms, patients who are homozygous for UGT1A1 *28 have a 7-fold higher risk of a serious adverse reaction, such as neutropenia, to irinotecan.

Around 10% of Japanese are homozygous for *28, homozygous for *6, or heterozygous for *28 and *6, so these polymorphisms are found in 1 in 10 people. People with these polymorphisms have a high risk of a serious adverse reaction to irinotecan.

A UGT1A1 polymorphism can be detected in normal cells as well, so in routine clinical practice blood is collected prior to treatment, and a kit is used to identify UGT1A1 gene polymorphisms *28 and *6. Results are received in about 2 weeks.

If a polymorphism is found, then the irinotecan will be roughly halved or another anticancer agent will be used.

Thus, genomic medicine for cancer helps to identify gene polymorphisms and to predict adverse reactions to anticancer agents.

Slide 7

Last is a depiction of genomic medicine for cancer in the future.

One could envision a shift from a diagnosis based on a conventional histologic classification by organ to the identification of specific gene abnormalities and a diagnosis by genetic mutation.

One could envision panel testing that identifies around 100 gene abnormalities and a comprehensive genetic analysis using next-generation sequencers that identifies 20,000–30,000 gene abnormalities. Treatment will increasingly be provided by selecting drugs that should be efficacious.
Now, I'd like to start brining my lecture to a close.

Slide 8
Here is a summary of what we have covered.
With this, I conclude my lecture.