The Realities of Genomic Medicine for Cancer: 1 Somatic mutations and cancer (1)
-Genomic abnormalities in non-hereditary tumors and their relationship to medicine-

Kyouichi Kaira　Gunma University

CH1.

Slide 1

I will be talking about the Realities of Genomic Medicine for Cancer: Somatic mutations and cancer. In specific terms, I will be talking about genomic abnormalities in non-hereditary tumors and their relationship to medicine.

Slide 2

I will start off by providing an overview of chemotherapy for cancer.　I will then explain the general realities of genomic medicine for cancer.　I will mainly be talking about driver mutations, molecularly targeted drugs, biomarkers, and liquid biopsy.

Slide 3

Cancer treatment consists of 3 pillars: surgery, radiation therapy, and chemotherapy.　However, immunotherapy has come to play an important role in cancer treatment as a result of recent advances in immunotherapy.

Slide 4

We use anticancer agents in chemotherapy, so I will now briefly explain anticancer agents.　An anticancer agent refers to a drug that inhibits the proliferation of cancer cells or that kills cancer cells. Altogether, there are around 100 oral and infused anticancer agents.　There are differences between anticancer agents and generics.　Anticancer agents have a narrower therapeutic range than generics and can readily cause adverse reactions or unexpected adverse events.　Moreover, there are vast individual differences in their efficacy and toxicity.

Slide 5

I will now explain the differences between anticancer agents and generics from the perspective of their therapeutic effectiveness and incidence of toxicities in accordance with the dose.　The figure on the left shows the efficacy and toxic response in accordance with the dose of a generic, but it clearly has a wider safety margin compared to the anticancer agent in the figure on the right.　Thus, generics have a wide safety margin while anticancer agents have a narrow safety margin.

Slide 6

Shown here is a classification of organ disorders by the therapeutic effectiveness of anticancer agents. A is a group who can be cured with chemotherapy (e.g. patients with hematologic malignancies), B is

a group whose life can be prolonged (e.g. patients with small cell lung cancer or breast cancer), C is a group whose symptoms can be alleviated and whose QOL can be improved (e.g. patients with non-small-cell lung cancer, head and neck cancer, or a gastrointestinal tumor), and D is a group that is expected to benefit little (e.g. patients with thyroid cancer).

Slide 7

Shown here are the general types of anticancer agents. Agents are mainly classified into 3 categories: chemotherapy agents, molecularly targeted drugs, and hormone therapies. Chemotherapy has cytotoxic action and causes intense adverse reactions.

Molecularly targeted therapies specifically target molecules associated with the infiltration, proliferation, or metastasis of cancer cells. Hormone therapy is used to treat forms of cancer such as breast cancer, endometrial cancer, and prostate cancer, and it causes relatively few adverse reactions.

Slide 8-9

I will now explain chemotherapy, which involves cytotoxic anticancer agents. As shown in the slide, these agents damage DNA in cancer cells and they inhibit cancer cell division. However, they also damage normal cells, so they pose a problem in terms of adverse reactions such as disordered hematopoiesis.

Slide 10

I will now explain the types of cytotoxic anticancer agents.

Alkylating agents such as cyclophosphamide alkylate DNA and inhibit DNA synthesis. Platinum-based drugs such as cisplatin bind to double-stranded DNA and inhibit DNA synthesis. Antimetabolites such as 5-FU act on the phase of the cell cycle when DNA synthesis occurs and inhibit DNA synthesis. Microtubule inhibitors such as paclitaxel and docetaxel inhibit microtubules involved in cell division. Topoisomerase inhibitors such as irinotecan and etoposide bind to DNA fragments during cell division.

Slide 11

I will now explain the thinking behind treatment with chemotherapy.

When a cytotoxic anticancer agent is administered, normal cells decrease but the cell count will recover over time. However, tumor cells recover slower than normal cells, so tumor cells will gradually decrease with repeated administration of an anticancer agent, and normal cells that decreased will recover. Thus, repeated sessions of chemotherapy reduce the damage to normal cells and readily reduce tumor cells.

Slide 12

The best treatment involves the use of a combination of cytotoxic anticancer agents with different

mechanisms of action. A cell cycle-specific drug is often combined with a cell cycle-non-specific drug. The standard treatment for lung cancer involves a combination of 2 agents, e.g. a platinum-based drug and a taxane, a topoisomerase inhibitor, or an antimetabolite. This is more therapeutically effective than monotherapy.

Slide 13

I will now explain molecularly targeted drugs. As I just explained, cytotoxic anticancer agents damage normal cells as well as cancer cells, as shown in the slide. Thus, they can cause intense adverse reactions. In contrast, molecularly targeted drugs stop the action of cancer cells by specifically attacking cancer cells. Thus, these drugs do little damage to normal cells and they efficiently kill cancer cells.

Slide 14

Shown here are examples of molecularly targeted drugs. ATRA has proven to be efficacious in treating acute myelogenous leukemia and imatinib has proven to be efficacious in treating chronic myeloid leukemia. Imatinib has also proven to be efficacious in treating a GIST. Rituximab is used to treat malignant lymphoma, and bortezomib is used to treat multiple myeloma. Gefitinib and erlotinib (EGFR-TKIs) are used to treat lung cancer, and particularly adenocarcinoma of the lung. Trastuzumab (a HER2 inhibitor) is used to treat breast cancer. Cetuximab (an anti-EGFR antibody) is used to treat colon cancer. Bevacizumab (an angiogenesis inhibitor) is used chemotherapy for colon cancer and lung cancer.

Slide 15

I will now briefly explain signalling by epidermal growth factor receptor (EGFR) while using EGFR as an example of a molecular target. A ligand known as epidermal growth factor (EGF) binds to a receptor known as EGFR. Afterwards, EGFR forms a dimer. Phosphorylation of a given tyrosine kinase in cells occurs, and RAS-RAF-MAPK is activated, causing cell proliferation. The PI3K-AKT pathway is activated, leading to the proliferation of cancer cells. The process by which a stimulating agent known as a ligand binds to receptors on the cell membrane and conveys information to cells is referred to as signalling.

Slide 16-17

I just explained EGFR. In 2004, mutations in EGFR were found to respond to an EGFR tyrosine kinase inhibitor (TKI). This finding was announced in the world's leading scientific journals such as the NEJM and Science. As shown in the slide, phosphorylation of tyrosine kinases must occur when signalling information is conveyed. When mutations occur in these tyrosine kinases, an EGFR-TKI can readily bind to them, block signalling, and inhibit the proliferation of cancer cells.

Slide 18-19

In EGFR mutation-positive patients, an EGFR-TKI readily binds to the ATP-binding site of tyrosine kinases, as I briefly explained a moment ago. As shown in the slide, a TKI binds to a tyrosine kinase and signalling is silenced. In EGFR mutation-negative patients, the ATP-binding site of tyrosine kinases precludes the binding of an EGFR-TKI. A TKI is unable to bind to a tyrosine kinase. Signalling cannot be disrupted, so cancer cells continue to proliferate. A mutation in the EGFR gene can be identified by subjecting tumor cell DNA to PCR.

Slide 20-22

This slide shows an EGFR-TKI blocking cancer signalling.

A ligand binds to EGFR and a signal is transmitted. Signalling is blocked by an EGFR-TKI and proliferation of cancer cells is inhibited. Thus, the EGFR-TKI is therapeutically effective.

Slide 23

When EGFR mutation-positive lung cancer was actually treated with gefitinib (an EGFR-TKI), the response rate was about 70%. When it was treated with a cytotoxic anticancer agent, the response rate was about 30%. When a molecule (i.e. EGFR) was targeted, therapeutic effectiveness was found to have at least doubled compared to chemotherapy.

Slide 24

A phase 3 trial compared an EGFR-TKI and standard treatment of EGFR mutation-positive lung cancer with a cytotoxic anticancer agent. Survival after each treatment was compared. As shown in the slide, the survival curve for patients receiving the EGFR-TKI (indicated in red) surpassed that for patients receiving chemotherapy (indicated in blue). Statistical analysis revealed that the EGFR-TKI significantly improved patient prognosis after treatment of EGFR mutation-positive lung cancer.

Slide 25

Shown here are chest X-ray findings when a patient actually received gefitinib (an EGFR-TKI).

On the left is an X-ray prior to treatment. Lung cancer is evident in the right lung and ascites due to carcinomatous pleurisy was noted. In the center is an X-ray 10 days after treatment. The opacity in the lung field has markedly diminished. On the right is an X-ray 10 days after treatment. The opacity has disappeared. Thus, patients who respond to an EGFR-TKI are often encountered in routine clinical practice.

Slide 26-27

This slide summarizes advances in chemotherapy for lung cancer.

In the 1970s, survival was 2 to 5 months with supportive therapy alone. Prognosis improved to 6 to 8 months with a platinum-based drug alone and to 8 to 14 months with combined therapy with a

platinum-based drug and a cytotoxic anticancer agent. I mentioned EGFR a moment ago. When a mutation in that molecule was detected and it was treated with an EGFR-TKI, prognosis improved dramatically to 2 to 3 years. Thus, genomic medicine for cancer is considered to be a promising treatment to substantially improve patient prognosis as well as QOL in routine clinical practice.