Chapter5

Slide 1

Next, I will describe an instance where a gene abnormality that will not respond to molecularly targeted drugs is identified in cancer cells and, conversely, the selection of patients who are likely to respond.

The gene abnormality in question is found in KRAS.

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The name Ras comes from rat sarcoma. RAS was identified as the product of an oncogene in the Harvey sarcoma virus and the Kirsten sarcoma virus, which are retroviruses that cause sarcoma in rats.

HRAS, NRAS, and KRAS are members of the RAS family.

The most frequent mutations are KRAS mutations, so I will explain about KRAS.

KRAS is protein consisting of 186 amino acids with a molecular weight of 21 kDa. There are 3 hotspots where a mutation is likely to occur in KRAS: codons 12, 13, and 61.

Mutations in these 3 codons account for 99% of all KRAS mutations.

The most prevalent is a mutation in codon 12.

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As I mentioned in the chapter on BRAF, the RAS family includes KRAS. RAS is located downstream of receptors such as EGFR, and it is an important molecule that facilitates stimulation of various signaling pathways, such as MAPK pathways with downstream RAF/MEK/ERK and PI3K/AKT/mTOR. When a mutation occurs in KRAS, downstream signaling is constantly activated despite the lack of signaling from receptors such as EGFR that are located upstream. The mutation promotes cell growth and survival.

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As shown here, a KRAS mutation is detected in various types of cancer. The mutation is detected in over 60% of pancreatic cancers, over 40% of colon cancers, and over 25% of adenocarcinomas of the lung.

Because of their relationship to treatment with molecularly targeted drugs, KRAS mutations must be assessed in colon cancer.

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Anti-EGFR antibodies are approved for treatment of colon cancer. Two, cetuximab (human-mouse chimeric antibody) and panitumumab (a human antibody), are used in Japan.

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These anti-EGFR antibodies only act on colon cancer cells with a KRAS mutation. I will now explain the mechanism by which they act.

In cancer cells with wild-type KRAS, ligands such as EGF, TGF-α, or amphiregulin bind to EGFR expressed on the cell membrane. As a result, downstream KRAS/RAF/MEK/ERK, i.e. MAPK pathways, are activated, and cells survive and proliferate. When anti-EGFR antibodies bind to EGFR under these conditions, they inhibit binding of a ligand to EGFR, so downstream signaling is inhibited, cancer cells die, and the efficacy of an anticancer agent is enhanced.

If, however, a KRAS mutation is present, then downstream MAPK pathways are constantly activated. Even if anti-EGFR antibodies are administered and bind to EGFR, downstream signaling is constantly activated, so an anticancer agent will have no effect.

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This fact was indicated clinically in the CRYSTAL trial.

The therapeutic effectiveness of standard chemotherapy alone was compared to that of standard chemotherapy with the anti-EGFR antibody cetuximab added for initial treatment of metastatic colorectal cancer (i.e. colon cancer).

A combination of anticancer agents known as FOLFIRI was used as standard chemotherapy.

A stratified analysis as part of that trial indicated that progression-free survival was significantly prolonged for patients with wild-type KRAS when cetuximab was added to standard chemotherapy compared to standard chemotherapy alone.

However, adding cetuximab had no benefit whatsoever for patients who were positive for a KRAS mutation.

Based on these results, adding anti-EGFR antibodies to standard chemotherapy resulted in no benefit for patients with KRAS mutation-positive colon cancer. Anti-EGFR antibodies are not used to treat patients with a KRAS mutation.

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Right now, there are no drugs that can treat a KRAS mutation, so a KRAS mutation is a biomarker of drug inefficacy.

Drugs to treat a KRAS mutation will be developed in the future, and research needs to continue so that a KRAS mutation can become a biomarker of drug response.