Cetuximab

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Cetuximab is a human/mouse chimeric monoclonal antibody targeting epidermal growth factor receptor (EGFR), first approved in the world.

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1. The History of Cetuximab

Cetuximab is used for the treatment of metastatic colon cancer, metastatic non-small cell lung cancer, and HNSCC. For colon cancer, cetuximab was first approved in Switzerland, USA, and EU from 2003 to 2004 as a second-line treatment for EGFR-positive unresectable advanced or recurrent colorectal cancer. In 2008, it was approved as a first-line treatment for EGFR-positive and KRAS wild-type colorectal cancer. On the other hand, for HNSCC, based on the results of the Bonner study in 2006, “cetuximab + RT” and “cetuximab single agent use after BRT” have been approved for LA-HNSCC [1]. In 2008, the results of the EXTREME study were published. For R/M-HNSCC, “Cetuximab + CDDP (or CBDCA) + 5-FU” was approved in many countries and was introduced to Japan in 2012 [2].

2. Current Trends of Cetuximab in LA-HNSCC and R/M-HNSCC

Cetuximab has been proven to be useful in various clinical trials in combination with radiotherapy and chemotherapy such as CDDP. The Bonner study compared 424 LA-HNSCC patients with two groups, the combination group (radiotherapy plus cetuximab) and radio-monotherapy group [1]. As a result, the median local disease control period was 24.4 months in the combination group and 14.9 months in the radio-monotherapy group (p = 0.005), and the median overall survival (OS) was 49.0 months and 29.3 months, respectively (p = 0.03). Therefore, the cetuximab combination group was significantly superior in local control and survival.

The EXTREME study compared 442 R/M-HNSCC patients with two groups, the FP alone group (CDDP/CBDCA + 5-FU) and the combination group (FP plus cetuximab) [2]. As a result, the median OS was 10.1 months in the combination group versus 7.4 months in the FP alone group (p = 0.04), and the median progression-free survival was 5.6 months and 3.3 months, respectively (p = 0.001). Thus, a significantly prolonged survival was shown in the cetuximab combination group.

In addition to the EXTREME study, clinical trials for R/M-HNSCC include the GORTEC 2008-03 trial (CDDP + DTX + cetuximab) [3], Hitt trial (Weekly PTX + cetuximab) [4], CSPOR-HN02 trial (PCE regimen; PTX + CBDCA + cetuximab) [5], and any other widely applied regimens.

3. Future Prospects of Cetuximab in HNSCC

High EGFR expression is said to be found in 25–77% of colon cancers and 90% or more of HNSCC [6][7], when ligands such as EGF and transforming growth factor-α (TGF-α) bind to EGFR, they form a dimer with EGFR or other human epidermal growth factor receptor (HER) family members. Therefore, autophosphorylation of the intracellular tyrosine kinase domain, and activating further downstream Ras-Raf-MAPK and PI3K-Akt pathways are deeply involved in cancer growth and metastasis.

Initially, cetuximab was used exclusively in colon cancer cases in which EGFR expression was observed in tumor cells by immunostaining, but subsequent studies showed good response rates in colon cancer cases in which EGFR expression was negative [8]. Therefore, it was clarified that the intensity of EGFR expression did not correlate with the therapeutic effect of cetuximab [9]. Currently, EGFR immunostaining is not recommended for determining the indication of anti-EGFR antibody [10]. Anti-EGFR antibody therapy for unresectable colon cancer was found to be ineffective in cases with RAS (KRAS/NRAS) gene mutations (about 40% of colorectal cancers), and RAS genetic testing was established as a companion diagnostic tool [11]. Recently, other genetic abnormalities, such as gene mutation of BRAF [12], PIK3CA [13], and EGFR extracellular domain (ECD) [14], gene amplification of HER2 [15] and mesenchymal-epithelial transition factor (MET) [16], have been reported as acquisition resistance factors of anti-EGFR antibody [17].

Although a biomarker for predicting the therapeutic effect of cetuximab has not been established in HNSCC, it has been suggested to be associated with rash, which is a typical adverse event of cetuximab. In an additional report from the Bonner study, OS in BRT patients was 25.6 months in the group with Grade 1 or lower rash, whereas it was 68.8 months in the group with Grade 2 or higher [18], indicating that the OS of the severe rash group was significantly superior. Furthermore, in the report by Saltz L et al., the response rate and disease control rate of the cases with skin disorders, such as rash, tended to be higher than the cases without rash, when cetuximab was applied to R/M-HNSCC [19]. Rash, which is a typical adverse event of cetuximab, is the most clinically easy-to-understand index and is attracting attention as a clue for the development of biomarkers in the future.

References

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