protein kinase, inhibiting cell proliferation. It has been also illustrated that cetuximab increases the receptor internalization which is another mechanism to silence the receptor. Cetuximab arrests cell cycle at G1 gap phase by upregulating anti-proliferative $p27^{kip1}$, which functions via complex formation with Cdk2, and downregulating proliferating cell nuclear antigen (PCNA). It also decreases angiogenic factors, inhibits tumor-cell invasion and metastasis via downregulation of matrix metalloproteinases (MMPs) and VEGF, and promotes apoptosis by upregulating apoptotic protein, Bax, with the help of other chemotherapeutic agents. Cetuximab has been widely shown to display synergistic effect with other agents and/or radiotherapy.

Binding of antigen-binding fragment (Fab) of Cetuximab, which displays higher affinity comparing to ligands of EGFR, takes place via domain III of extracellular EGFR, preventing the receptor from conformational change to be dimerized and blocking EGFR signaling through inhibition of EGF and TGF-alpha-stimulated phosphorylation of the receptor.

Pharmacokinetics and Pharmacodynamics

In a study conducted by Fracasso et al., patients with colorectal, breast, and head and neck carcinomas were administered with one of different dosages of cetuximab (50, 100, 250, 400 and 500 mg/m^2). For each concentration, cetuximab serum concentration was showed to reach maximum at 3 h, and decrease slowly. Serum concentration decreased to baseline at 96 h and 168 h for dosages 50 and 100 mg/m^2, respectively. Mean maximum observed concentrations (C_{max}) increased in a dose dependent manner (from 22.8 ug/ml to 245.6 ug/ml).

It was indistinguishable for 400 mg/m^2 (C_{max}=228.9 ug/ml) and 500 mg/m^2 (C_{max}=245.6 ug/ml). The mean total body clearance based on body surface area for cetuximab was similar following doses of >100 mg/m^2 (range, 34.4-19.3 L/h/m^2) but greater in the 50 mg/m^2 dose group (65.9 L/h/m^2). Biopsy results showed that maximal cytoplasmic EGFR downregulation after treatment was seen in 8 h with 400 mg/m^2 dosage.

After 250 mg/m^2 weekly cetuximab administration, the average trough level of patients with both partial responses (PRs) and stable disease (SD) was 60,742 ng/ml (~400 nmol/l) compared with those patients with progressive disease (PD; 33,208 ng/ml). In another study, cetuximab was infused as loading dose of 400 mg/m^2 followed by weekly infusions of 250 mg/m^2 in colorectal cancer patients. Median residual concentrations were 41 and 54 mg/L on days 14 and 28, respectively. It was determined that initial serum albumin concentration was significantly related to first-order elimination clearance of cetuximab. Central volume of distribution was 2.96 L (4%), peripheral volume of distribution was 4.65 L (6%), elimination clearance was 0.479 L/d (4%) and distribution clearance was 0.836 L/d (8%).

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