Clinical Trials

**Major finding:** Adding gemtuzumab ozogamicin to standard induction therapy improves outcome.

**Approach:** Fractionated lower doses of gemtuzumab ozogamicin were used to minimize toxicity.

**Impact:** Gemtuzumab ozogamicin should be reassessed as a first-line therapy for AML.

GEMTUZUMAB OZOGAMICIN IS AN EFFECTIVE FIRST-LINE AML THERAPY

Systematic cytotoxic treatment with daunorubicin and cytarabine has been the standard induction regimen for patients with acute myeloid leukemia (AML) for decades, but targeted delivery of cytotoxic agents to leukemia cells may improve clinical outcome. In previous phase II and III clinical trials, the combination of gemtuzumab ozogamicin, a humanized anti-CD33 antibody conjugated to calicheamicin, with standard induction therapy elicited a complete response in some relapsed AML patients, but higher doses were associated with hematologic and hepatic toxicity and increased induction death. Castaigne and colleagues hypothesized that administration of fractionated low doses of gemtuzumab ozogamicin would minimize toxicity while allowing delivery of higher cumulative doses. Treatment-naïve AML patients, ages 50 to 70 years, without previous myeloproliferative or myelodysplastic syndrome were enrolled in a randomized, open-label phase III study comparing standard induction therapy with daunorubicin and cytarabine to standard induction therapy with three 3-mg/m² doses of gemtuzumab ozogamicin every 3 days (3-3-3 regimen). After induction therapy, the complete response rates were similar between the 2 groups (81% in the gemtuzumab ozogamicin group and 75% in the control group), but after 2 years, event-free survival, overall survival, and relapse-free survival were all significantly increased in the gemtuzumab ozogamicin group (40.8%, 53.2%, and 50.3%, respectively) compared with the control group (17.1%, 41.9%, and 22.7%, respectively). Of note, the benefit associated with gemtuzumab ozogamicin was most pronounced in patients with favorable or intermediate cytogenetics or FLT3 internal tandem duplication. The most frequent adverse events associated with gemtuzumab ozogamicin were delayed platelet recovery and persistent thrombocytopenia after chemotherapy, but the risk of treatment-related death was not increased. These findings suggest that the addition of fractionated low doses of gemtuzumab ozogamicin to standard induction therapy should be considered for older patients with de novo AML.


Tumor Suppressors

**Major finding:** Loss of intestinal Lrig1 expression leads to highly penetrant duodenal adenomas.

**Mechanism:** LRG1 negatively regulates ERBB signaling to maintain intestinal stem cell homeostasis.

**Impact:** The mutation and downregulation of LRIG1 observed in human cancers may drive tumorigenesis.

LRIG1 REGulates INTESTINAL STEM CELL QUIESCENCE

Intestinal stem cell homeostasis is critical for maintaining the continuously self-renewing intestinal epithelium while suppressing neoplastic growth. Through lineage tracing in the small intestine and colon of mice, Powell and colleagues identified a population of intestinal stem cells marked by expression of leucine-rich repeats and immunoglobulin-like domains 1 (Lrig1), which encodes a negative regulator of ERBB family receptor tyrosine kinases. LRG1-positive intestinal stem cells were distinct from the previously characterized, highly proliferative leucine-rich repeat containing G protein-coupled receptor 5 (LRGR5)-positive stem cell population, with a low proliferative index and a gene expression profile enriched for cell-cycle inhibitors and other markers of quiescence. To determine whether LRG1-expressing cells could initiate tumor growth, the authors conditionally deleted one allele of adenomatous polyposis coli (Apc), a tumor suppressor gene that is commonly inactivated in colorectal cancer, in LRG1-expressing cells of the small-intestinal and colonic epithelia. Upon Apc deletion, 100% of the mice developed intestinal tumors in sites from the duodenum to the distal colon; as expected, the second Apc allele was lost in the tumors. LRG1 itself was also implicated in tumor suppression, as deletion of Lrg1 from birth resulted in a significant increase in ERBB1-3 protein levels and ERK phosphorylation in the intestinal crypt epithelia. In addition, duodenal adenomas developed in 88% of mice by the age of 5 to 6 months. As cancer genome sequencing efforts have identified mutations in LRIG1 in subsets of human colorectal cancer and glioblastomas, these findings suggest that deregulated stem cell homeostasis and derepression of ERBB signaling due to LRIG1 inactivation may be a driving event in human cancers.

LRIG1 Regulates Intestinal Stem Cell Quiescence


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