



# Multidisciplinary Therapy for Advanced Gastric Cancer



Kei Horino<sup>1</sup>, Hideo Baba<sup>2</sup> and Shinya Shimada<sup>1\*</sup>

<sup>1</sup>Department of Surgery, Kumamoto General Hospital, Japan

<sup>2</sup>Department of Gastroenterological Surgery, Graduate School of Life Sciences, Japan

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**\*Corresponding author:** Shinya Shimada, Department of Surgery, Kumamoto General Hospital, Japan Community Health Care Organization, Kumamoto, 10-10 Tohri-cho, Yatsushiro, Kumamoto 866-8660, Japan, Email: [shimada-shinya@kumamoto.jcho.go.jp](mailto:shimada-shinya@kumamoto.jcho.go.jp)

## Opinion

Whereas the prognosis of gastric cancer has improved markedly due to developments in surgical methods and perioperative treatment, advanced gastric cancer progresses rapidly, and its prognosis is still miserable. Surgery for gastric cancer has changed greatly in the 100 years since Billroth conducted the first distal gastrectomy, and it is now possible to reduce the invasiveness of surgery for gastric cancer by performing laparoscopic surgery. In addition, we are now able to operate via remote control using robotic surgery, and extended resection procedures for advanced gastric cancer have been standardized, which has markedly improved their safety and accuracy. In gastric cancer patients that only suffer peritoneal dissemination, better results can be obtained by performing extensive intraoperative peritoneal lavage (EIPL) after curative gastric resection.

However, there are no effective treatments for cases of very advanced gastric cancer involving remote metastasis. Recently, great advances have been made in chemotherapy for gastric cancer. In particular, molecular targeted therapy, which was initially used to treat lung cancer, breast cancer, and malignant melanoma, has significantly improved the prognosis of advanced gastric cancer. In the first stage of molecular targeted therapy for gastric cancer, human epidermal growth factor receptor 2 (HER2) was targeted. HER2 is a protein found on the surfaces of cancer cells and contributes to cancer cell growth. Thus, cancer cell growth can be restrained by administering an anti-HER2 antibody, which inhibits signal transduction from HER2. In patients with HER2-positive gastric cancer, this therapy proved to be effective when used in combination with cisplatin and 5-FU. However, as only around 20-30 % of gastric tumors are HER2-positive this molecular targeted therapy is not effective in all gastric cancer patients. In the second stage of molecular targeted therapy for gastric cancer, tumor-feeding-

vessel growth factors that are involved in tumor genesis were targeted. Drugs that target the epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), etc., have already been commercialized and are used all over the world. In particular, the prognosis of colon cancer has been significantly improved by the use of chemotherapy involving these molecular targeting drugs. On the other hand, only anti-VEGF therapy with irinotecan has been effective against gastric cancer. It seems that this discrepancy is caused by the heterogeneity of gastric cancer.

Subsequently, molecular targeting therapies that targeted immunological molecules were developed. Programmed cell death-1 ligand-1 (PD-L1) is one of the molecules expressed on cancer cells. It binds to Programmed cell death protein-1 (PD-1), which is T-cell surface receptor, and inhibits T-cells activities against cancer cells. Therefore, anti-PD-L1/PD-1 therapy restores the effects of T-cells against cancer cells by preventing PD-L1/PD-1 from functioning. Molecular targeting therapies in which antibodies are used to target the immune system are called immunotherapies. They have been used to treat advanced gastric cancer, and their anti-cancer effects have been established.

Unlike conventional anti-cancer therapy, the adverse effects of immunotherapies vary. The onset of autoimmune disease like thyroid disease, autoimmune pancreatitis, and hepatitis, which can affect the whole body, due to hyper immunization is an important potential complication of immunotherapy. However, immunotherapy is comparatively safe to use because myelosuppression is not required. As various therapies for advanced gastric cancer have become established around the world, and novel treatments have recently appeared, we surgeons should not only perform surgery as a last resort, but also as part of modern multidisciplinary treatment for gastric cancer.



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