onstrate that NDV-GFP could be used diagnostically.

WHAT IS NEXT FOR THE IMPROVEMENT OF INTRAPERITONEAL DIAGNOSIS?

As described above, numerous efforts have been made to improve the detection of intraperitoneal free cancer cells. The purpose of most of these studies appeared to primarily be an improvement of the accuracy in cytology. The secondary purpose will be to make diagnosis more convenient and automatic than subjective conventional cytology. Once the accuracy and procedure is essentially improved over the conventional cytology, what should we do next? The identification of intraperitoneal free cancer cells confers poor prognosis. In patients with positive cytology without macroscopic peritoneal metastasis, the benefit of radical or aggressive surgery is still a matter of debate. While some of these patients are palliated, others may undergo more aggressive therapies. Along with the improved diagnostic modality, the treatment strategy would also have to be a coupled issue.

MULTIMODAL CLINICAL APPROACH FOR PERITONEAL SPREAD OF GASTRIC CANCER

Surgeons have witnessed some patients with peritoneal spread of gastric cancer who underwent radical surgery and experienced cures due to the recent improvements in multimodal treatment. A phase II study of whether gastrectomy with curative intent would be beneficial for patients with positive cytology but absence of macroscopic peritoneal seeding has been conducted[63,64]. The study showed that median overall survival time was 705 d, and the 5-year survival rate was 26% in the patients with positive cytology with no other non-curative factors, suggesting that surgery with curative intent could be indicated even for patients with positive cytology[63,64]. For gastric cancer patients with macroscopic peritoneal metastasis, Yamaguchi *et al*[65] evaluated intraperitoneal chemotherapy along with systemic chemotherapy as a phase II study. They reported a 1-year survival rate of 77.1%, which is surprisingly high. The same group also reported salvage gastrectomy after intravenous and intraperitoneal chemotherapy for the patients who had peritoneal metastasis but showed apparent shrinkage of their peritoneal nodules as well as negative cytology by the treatment[66]. Those patients who underwent salvage gastrectomy exhibited a 26.4-mo median survival period and 82% 1-year overall survival. Those results suggested that the more sensitive and specific peritoneal diagnosis with the molecular approach might allow gastric cancer patients to receive more suitable individualized multimodal therapies.

A NEW MOLECULAR-TARGETING THERAPY FOR INTRAPERITONEAL SPREAD OF GASTRIC CANCER

Along with the research for the improvement in detection of intraperitoneal cancer cells, molecular targeting therapies might be derived from the results of basic research. One of the molecular targets is epithelial cell adhesion molecule (EpCAM), a type I transmembrane glycoprotein functioning as a homotypic intercellular adhesion molecule[67]. High-level EpCAM expression was observed in 90.7% of gastric cancer[68]. Catumaxomab is an artificially engineered, tri-functional bispecific monoclonal antibody; Fab binding sites bind to EpCAM on cancer cells and CD3 on T cells, and the Fc region binds and activates accessory immune cells. The tri-cell complex of T-cells, tumor cells and accessory cells induces MHC-unrestricted but specific efficient tumor cell killing. The therapeutic benefit of Catumaxomab for patients with malignant ascites including gastric cancer patients has been reported in a pivotal clinical trial[69], which led to approval of Catumaxomab by the European Medicines Agency (EMA) in 2009. Intraperitoneal Catumaxomab treatment has been shown to trigger the activation of immune effector cells in the peritoneal cavity resulting in the depletion of EpCAM-positive tumor cells[70]. Thus, local strategies with molecular targeting agents might represent the appropriate option for treatment of the peritoneal spread of gastric cancer.

CONCLUSION

In the past decade, enormous strides have been made in the research for molecular detection of intraperitoneal free gastric cancer cells, and many new strategies have been clinically tested in gastric cancer patients. As with the conventional cytology, none of the candidate alternatives to conventional cytology are a perfect modality yet, whereas most of them would potentially be conducive to improve the conventional diagnosis and to predict prognosis. The uncertainty of a definition of positivity in these novel approaches and their clinical relevance remain potential limitations to the practical clinical use of these technologies. Too highly sensitive techniques such as PCR may result in the detection of clinically irrelevant metastatic disease, which could lead to either overtreatment with unnecessary chemotherapy, or worse, the withdrawal of potentially curative surgical treatment. Nevertheless, the development of more sensitive and rapid diagnostics in evaluating minimal peritoneal disease is needed for patients to be properly treated. Since peritoneal lavage cytology has recently been included in the staging criteria of gastric cancer, the cytology diagnosis has been focused on as having an important predictive

role in gastric cancer treatment, and the molecular diagnosis has undergone tremendous challenges. With the accumulated evidence, the molecular diagnosis of peritoneal cytology may be a reality in future gastric cancer practice.

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