Scientific Programme
Invited Abstracts

Saturday 28 September 2013

Special Lecture (Sat, 28 Sep, 08:00−08:45)
Limitation and Indication of Minimally Invasive Surgery for Gastric Cancer

1 INVITED

Limitation and indication of minimally invasive surgery for gastric cancer

K. Maruyama[1]. [1]*University of Health and Welfare Sanno Hospital, Department of Surgical Oncology, Tokyo, Japan*

Early stage gastric cancer is remarkably increasing by development of diagnostic methods and mass-screening system. Proportion of Stage-I cancer increased from 22.5% (1963−66) to 57.3% (2008) in Japanese Nationwide Registry.
According to the increase of early stage cancer and demand for high quality of life, the surgical treatment was shifted from "high radicality" to "minimally invasive surgery with enough curability, high safety, and high quality of life". Such attitude leads to wide variation of the surgical treatments as follows. Intention of "endoscopic mucosal resection" and "endoscopic submucosal dissection" is to avoid disadvantages and risks of gastric resection and to get quick recovery. The indication is for a cancer with definitely no node metastasis. The requirements are a) mucosal cancer, b) no ulcer scar and elevated or flat lesion, c) 2.0 cm or less in diameter, c) well or moderately differentiated carcinoma. Accurate preoperative diagnosis is essential. And we never hesitate to shift gastric resection if the requirements are not met. Intention of "laparoscopic resection" is to avoid disadvantages and risks of open gastric resection and to get quick recovery and cosmetic advantage. This procedure includes "laparoscopic wedge resection", "laparoscopic resection", and "robotic surgery". The indication was for an early stage cancer, but it is now expanded to advanced cancer according to development of the instruments and surgical skills. In the Japanese Nationwide Survey, more than 7,000 patients were treated every year in 2009, 2010, and 2011. Proportion of distal gastrectomy with D2 standard lymphadenectomy was 51.8%, distal gastrectomy with D3 extended lymphadenectomy was 20.6%, and total gastrectomy was 16.5% in 7400 cases (2011). Robotic surgery showed high accuracy and radicality in surgical procedures, and is now remarkably increasing in Korea and Japan.
"D2 systematic lymphadenectomy" was the gold standard for Japanese and most world leading surgeons, but the attitude was changed to "lymphadenectomy with limited or reasonable extent". The Intention is to reduce postoperative complications and nutritional disadvantages. Intention of "sentinel node navigation" is to detect metastatic nodes and to avoid disadvantages by unnecessary node dissection. This technique is indicated for potentially curatively resectable cancer, and most trials are now for early cancer during laparoscopic resection. The tracers are blue dye, fine carbon particle emulsion, oil contrast media, radioactive mm99 Tin colloid, and CEA antibody. The high detectability was reported; 96% of metastatic nodes were found in the hot nodes. The essential progress are to "develop cancer specific tracer" and to "improve accuracy of frozen histological examination".
We have to know that the most important patient's demand is "cure from cancer". We have to understand the scientific base of minimally invasive surgery and should avoid increase of recurrence caused by the indication expansion.
No conflict of interest.

Opening Session (Sat, 28 Sep, 09:00−11:00)
Biological Basis of Personalised Cancer Therapy

2 INVITED

Lgr5 stem cells in self-renewal and cancer

H. Clevers[1]. [1]*Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences & University Medical Centre Utrecht, Utrecht, Netherlands*

The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. We originally defined *Lgr5* as a Wnt target gene, transcribed in colon cancer cells. Two knock-in alleles revealed exclusive expression of *Lgr5* in cycling, columnar cells at the crypt base. Using an inducible Cre knock-in allele and the Rosa26-*LacZ* reporter strain, lineage tracing experiments were performed in adult mice. The *Lgr5*$^{+ve}$ crypt base columnar cells (CBC) generated all epithelial lineages throughout life, implying that it represents the stem cell of the small intestine and colon. Similar obserations were made in hair follicles and stomach epithelium.
Single sorted *Lgr5*$^{+ve}$ stem cells can initiate ever-expanding crypt-villus organoids in 3D culture. Tracing experiments indicate that the *Lgr5*$^{+ve}$ stem cell hierarchy is maintained in these organoids. We conclude that intestinal crypt-villus units are self-organizing structures, which can be built from a single stem cell in the absence of a non-epithelial cellular niche. The same technology has now been developed for the *Lgr5*$^{+ve}$ stomach stem cells.
Intestinal cancer is initiated by Wnt pathway-activating mutations in genes such as APC. As in most cancers, the cell of origin has remained elusive. Deletion of APC in stem cells, but not in other crypt cells results in progressively growing neoplasia, identifying the stem cell as the cell-of-origin of adenomas. Moreover, a stem cell/progenitor cell hierarchy is maintained in early stem cell-derived adenomas, lending support to the "cancer stem cell"-concept.
Fate mapping of individual crypt stem cells using a multicolor Cre-reporter revealed that, as a population, Lgr5 stem cells persist life-long, yet crypts drift toward clonality within a period of 1−6 months. Lgr5 cell divisions occur symmetrically. The cellular dynamics are consistent with a model in which the resident stem cells double their numbers each day and stochastically adopt stem or TA fates after cell division. Lgr5 stem cells are interspersed between terminally differentiated Paneth cells that are known to produce bactericidal products. We find that Paneth cells are CD24+ and express EGF, TGF-a, Wnt3 and the Notch ligand Dll4, all essential signals for stem-cell maintenance in culture. Co-culturing of sorted stem cells with Paneth cells dramatically improves organoid formation. This Paneth cell requirement can be substituted by a pulse of exogenous Wnt. Genetic removal of Paneth cells in vivo results in the concomitant loss of Lgr5 stem cells. In colon crypts, CD24+ cells residing between Lgr5 stem cells may represent the Paneth cell equivalents. We conclude that Lgr5 stem cells compete for essential niche signals provided by a specialized daughter cell, the Paneth cell.
No conflict of interest.

3 INVITED

The genetic basis for cancer therapy − the opportunity and the challenges

W.R. Sellers[1]. [1]*Novartis Institutes for BioMedical Research, VP/Global Head of Oncology, Cambridge, USA*

Cancer is fundamentally a disease driven by the acquisition and clonal selection of genomic alterations. These genetic changes result in the gain- and loss-of-function of oncogenes and tumor suppressor genes that together cooperate to induce and maintain the transformed state. Therapeutics directly targeting these underlying perturbations have now shown marked single-agent clinical activity in a diverse set of solid and hematologic malignancies well beyond the initial genetically targeted therapy paradigm established by imatinib in CML. Indeed, the efficacy of inhibitors of BRAF, MEK, ALK, EGFR, PDGFR, KIT and ABL mark the emergence of a new generation of highly active cancer therapeutics all taking advantage of the link to the underlying genetic drivers. There is now a significant opportunity to see greater clinical benefit by the utilization of targeted therapeutics in combination both within this space and with chemotherapy and immunotherapy.
Nonetheless, there are significant challenges to more fully realizing this paradigm broadly across all cancers. First, we remain hampered by an incomplete understanding of the genetic alterations characteristic of human cancer. Here, the advent of Next Gen Sequencing promises to allow us to probe the cancer genome at sufficient depth to understand the genetic combinations that enact each cancer type, to understand disease progression from benign to highly refractory states and to understand disease heterogeneity. Second, there have been significant hurdles in developing therapeutics that reverse the activity of non-kinase oncogenes (e.g. RAS and MYC) or reverse the activity of tumor suppressor mutations (e.g. p53, RB1). Third, the development of resistance to targeted therapy remains a problem for the field and this is related to the fourth issue, specifically the need to rapidly identify highly active novel combination therapy regimens and test these early in clinical development. Finally, there has been a chronic lack of a robust pre-clinical translational infrastructure that would allow for the more accurate prediction of human clinical trial results and hence improve the overall clinical trial success rate while shortening the time to maximizing patient benefit.
The aforementioned challenges to this promising field can be met, however, by an increasingly sophisticated set of experimental and therapeutic approaches. Examples of these approaches will be highlighted in the presentation.
Conflict of interest: *Ownership: Novartis Pharmaceuticals. Other substantive relationships: Employee of Novartis Pharmaceuticals*