Pathogenesis and treatment of Gastric Carcinoma: "An up-date with brief review"

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Abstract

Gastric cancer is one of the most common cancers and most frequent causes of cancer related deaths in the world. The overall survival rate is 15-20%. Although incidence is declining, its prognosis remains poor. The etiological factors and pathogenesis of gastric cancer are not yet fully understood. The integrated research in molecular pathology clarified the details of genetic and epigenetic abnormalities of cancer-related genes in the course of development and progression of gastric cancer. Although epidemiological evidences indicate that environmental factors play a major role in the carcinogenesis, the role of immunological, genetic and immunogenetic factors are thought to contribute to etiopathogenesis of gastric carcinoma. In addition to better understanding of pathogenesis of gastric cancer, the incidence, diagnostic studies and the therapeutic options have also undergone important changes in the last decade. There is ongoing debate regarding the role of adjuvant treatment. In advanced disease, palliation of symptoms, rather than cure, is the primary goal of patient management. Several combination therapies have been developed and have been examined in phase III trials; however, in most cases, they have failed to demonstrate a survival advantage over the reference arm. This review provides an appraisal of the published data related to concepts of molecular biology on gastric carcinogenesis and the new important recommendations for the management of patient with gastric carcinoma.

INTRODUCTION

Gastric carcinoma remains a common disease world-wide with a dismal prognosis. It represents the fourth most frequent malignancy and second leading cause of cancer related death worldwide ([1], [2]). The 5 year survival rate for gastric carcinomas is low (10-20%) ([3], [4], [5]). Over the past 15 years, research in molecular pathology has given us the understanding of genetic and epigenetic abnormalities of cancer related genes in the course of development and progression of gastric cancer. The last decade has also noticed multidisciplinary strategies for patients with localized gastric cancer and improved systemic therapies for patients with advanced disease.

ETIOPATHOGENESIS

Gastric cancer, like other cancers is the end result of the interplay of many risk factors as well as protective factors. Environmental and genetic factors are also likely to play a role in the etiology of the disease. Among the environmental factors, diet and infection with Helicobacter pylori are the most common suspects in gastric carcinogenesis. Various epidemiological and pathological studies have suggested that gastric carcinogenesis develops with the following sequent ional steps; chronic gastritis; atrophy; intestinal metaplasia; and dysplasia. The initial stages have been linked to excessive salt intake ([6]) and infection with H pylori ([7]). Genetic factors play important role in gastric carcinogenesis; leading to either abnormal genes over expression or inappropriate expression of normal genes, whose products confer the malignant phenotype. Advances have been made in the genetic changes mostly of the intestinal type; its development is probably a multistep process. The most common genetic abnormalities in gastric cancer tend to be loss of heterozygosity of tumor suppressor genes, particularly of p53 or "Adenomatous Polyposis Coli" gene ([8]). The latter leads to gastric oncogenesis through changes related to E-cadherin-catenin complex, which plays a critical role in the maintenance of normal tissue architecture. Mutation of any of its components results in loss of cell-cell adhesion, thereby contributing to neoplasia. E-cadherin/CDH1 gene germline mutations have been recognized in families with an inherited predisposition to gastric cancer of the diffuse type. Amplification and/or over expression of putative trophic factors have also been observed in gastric cancer. Serial analysis on gene expression (SAGE) performed on typical gastric cancer

tissues, compared gene expression profiles among them or with those in normal gastric tissue and identified specifically up regulated and down regulated genes. They selected about 60 genes which were detected in their gastric cancer libraries and examined the expression of these genes in normal human tissues by real-time polymerase chain ([9]). Polymorphisms of genes, whose expression is highly altered in cancer, may be candidates for novel risk factors and this information will be useful for cancer prevention

SURGERY

The only potentially curative treatment for localized Gastric cancer is complete surgical resection. A sub-total or total gastrectomy with an enbloc lymph node dissection is the standard treatment but even with optimal surgical resection, the prognosis remains modest in the western world. More extensive lymph node dissection, adjuvant radiotherapy and adjuvant chemotherapy did not result in survival benefits in randomized trails. Only post operative chemo-radiotherapy has been proven to be valuable in prospective randomized trials but the key issues demanding an answer are the optimization of surgery, radiotherapy and chemotherapy and whether chemo-radiotherapy will benefit survival or loco-regional control in the case of optimal surgery with an over D1 lymphadenectomy and without spleenectomy. ([10])

Published evidence regarding the role of surgery has brought a clear identification of standard procedures to be performed in surgical treatment of gastric cancer patients. Either total or partial gastrectomy proved to represent a correct and equivalent surgical approach with no differences in global outcome between these two modalities ([11]). However it is more difficult to establish the role of extended lymph node dissection (D2) in these patients which is favored by Japanese researches ([12]) and at the same time it is note-worthy to mention about two trials which failed to prove a survival advantage of classic D2 lymph node dissection over the D1 ([11, 13, 14]) Therefore the question whether a D2 resection should be preferred to D1 remains controversial. ([15, 16])

ADJUVANT AND NEOADJUVANT THERAPIES

Lymph node metastasis represents an important prognostic factor in radically resected gastric cancer patients with 5 year survival rate for these patients approaching 20-30%. This data forms a strong rationale for the use of adjuvant chemotherapy. There is a conflicting data from randomized clinical trials regarding the role of adjuvant chemotherapy after complete resection of gastric or gastro-esophageal junction adenocarcinoma ([17, 18, 19, 20, 21]). Although no difference in over all survival has been generally observed in older trials conducted between 1965-1985 and in several sub sequent studies ([11,22,23]), some positive trials were also presented renewing the interest for the role of post operative chemotherapy in resected gastric cancer patients ([24,25,26]). The challenge today for investigators is how best to incorporate the lessons learned from the recent successes of various trials like Intergroup 0116 trial And the Medical Research Council's (MRC) Magic trial.

The excellent results of North American Intergroup 0116 trial have led to the adoption of chemo-radiation a standard adjuvant therapy in North America ([27]).In this trial Macdonald et al randomized 556 patients to surgery followed by 5FU/Folinic Acid (FA) and 45Gys of external beam radiotherapy. The median overall survival in the surgery alone group was 27 months compared with 36 months in the chemo radiotherapy group, the hazard ratio for death being 1.35 (95% CI, 1.09-1.66; p=0.005). This study has been criticized in Europe because of lack of standardized surgery resulting in over 50% of patients having D0 dissection (less than complete dissection of N1 nodes). A subsequent analysis showed that the survival benefits of pot-operative chemo radiotherapy were retained in patients who had either D0 or D1 dissection ([28]). This supports the administration of post-operative chemo-radiation to patients regardless of whether adequate or inadequate lymph node dissection has been performed. As a result of the magnitude of the survival benefit seen, adjuvant chemo radiotherapy has become a standard of care in North America. However, some recent articles state that more randomized trails are needed to confirm the findings of the North American Intergroup trial 0116 before being adopted every where as the standard of care. ([29]).

The MRC's adjuvant gastric infusional chemotherapy (MAGIC) trial of perioperative chemotherapy was performed to determine its impact on patient outcomes ([30]). Five hundred and three (503) patients were randomized to receive 3 cycles of epirubicin, cisplatin and 5FU (ECF), before and after surgery; or surgery alone. Preliminary analysis after a median 2 years follow up showed statistically significant improved progression-free survival and strong trend towards improved overall survival. These positive results would suggest that a neoadjuvant approach be considered a part of future trials. The theoretical advantages are earlier treatment of metastasis and avoiding postoperative delays in chemotherapy in addition to down-

staging of tumors. The optimal choice for perioperative therapy will be addressed by the MAGIC 2 study, where the planned randomization is between perioperative chemotherapy and post operative chemo radiotherapy. Neoadjuvant combined chemotherapy and radiotherapy approach has also been demonstrated by Ajani et al([31]),but phase III evidence is wanting.

ADVANCED/METASTATIC DISEASE

The prognosis for patients with advanced gastric cancer is poor with a median survival of 3-5 months with best supportive care alone ([32]). Various chemotherapy combinations have been tried, eventually resulting in the development of ECF (epirubicin, cisplatin and continuous 5FU infusion) as a current standard treatment resulting in median survival of 8-9 months([33]).While the long term survival remains low hence the need for further clinical trials with novel agents and combinations. One new agent which has found a place in GI cancers is capecitabine- an oral prodrug form of 5FU. The advantages of this drug include easy administration and equivalent activity to infused 5FU. The currently accruing UK National Cancer Research Institute (NCRI) trial REAL2, has a 2x2 factorial design testing the substitution of oxaliplatin for cisplatin, and capecitabine for 5FU, against ECF in patients with advanced oesophagogastric adenocarcinoma. This study includes 1000 patients and will define the role of oxaliplatin and capecitabine in these patients.

NOVEL TARGETED THERAPIES

The biology of advanced gastric cancers is well characterized but it lies behind other more prevalent tumors in the exploration of targeted therapies. However, their clinical and biological behavior makes them a perfectly appropriate tumor population for targeted therapy. Various therapeutic strategies include EGFR inhibitors, antiangiogenic agents, cell cycle inhibitors, apoptosis promoters, matrix metalloproteinase's inhibitors and targets for immunotherapy and gene therapy. Marimastat, a matrix metalloproteinase (MMP) is the only agent that has reached the most advanced clinical development showing clear survival benefit in patients with advanced gastric cancer. This was shown by the results of a phase III study in which patients with advanced gastric cancers and gastro esophageal junction cancers were treated with Marimastat and compared with placebo with the primary objective being to demonstrate an advantage in the median OS for those patients allocated to receive Marimastat ([34]). Although this was the first demonstration of the therapeutic benefit for a MMPI in cancer patient, no further development of Marimastat has been done in this population. Other agents are still in initial clinical development, but their encouraging activity has prompted more extensive evaluation. EGFR inhibitors such as matuzamub, gefitinib, erlotuinib, angiogenic inhibitors like bevacizumab, and cell cycle inhibitors like flavopiridol and apoptosis promoters such as bortezomib are at the forefront of current clinical development. Biological response modifiers are also widely used for cancer therapy. The role of gene therapy is currently limited due to lack of specificity for tumor cells. Nevertheless some studies showed the feasibility of epithelial cell adhesions molecule (EpCAM) targeted adenoviral vectors in gastric and esophageal cancers. Consequently, patients with advanced gastric cancers should be considered for inclusion in clinical trial of targeted therapies in search for more effective treatment.

At present a survival predictor model based on identification of genes (CD36, SLAM, and PiM-1) has been proposed, having a specificity of 80% and sensitivity of 73.3%. And as such it has the potential to serve as a useful prognostic marker.

CONCLUSION AND PERSPECTIVES

The integrated research in molecular pathology has clarified the details of genetic and epigenetic abnormalities of cancer in the course of development and progression of gastric cancer. A custom-made assay named Ex-STOMACHIP, consisting of 395 genes identified by SAGE, is useful to study molecular stomach carcinogenesis and to obtain information about biological behavior and sensitivity to therapy in clinical setting. The combination of gene expression profiling and determination of genetic polymorphism will allow characterization of individual cancers and patient, leading directly to personalized medicine and cancer prevention.

The control of loco regional disease in gastric cancer patients is difficult to achieve. The extent of surgery and role of adjuvant therapies are areas of intense research and debate. The conflicting results reported in the literature might have been due to inadequate surgery, which could have resulted in a high proportion with residual tumor, the low number of patients recruited in most of the trials and the low activity of the chemotherapy drugs used.

Cisplatin and fluorouracil have been for decades the backbone of gastric-cancer chemotherapy treatment. The new drugs like irinotecan, oxaliplatin and taxanes have

provided better results in the metastatic setting. Some phase II studies recommend the combination of docetaxel and capecitabine as a highly active combination as first line chemotherapy for advanced gastric cancer. Capecitabine alone is unique among currently available treatments for advanced gastric cancers in that it is compatible with oral, patient oriented, home based therapy and as good as infusional 5FU therapy.

Some authors still believe that there may be a place for D1 dissection as standard treatment for gastric cancer .The Pan-European Trial in Adjuvant Colon Cancer (PETACC) Cooperative group is planning an international adjuvant trial comparing D1 surgery plus chemo radiation therapy with taxanes. Pre-operative chemotherapy could be added to both arms if MAGIC results become positive for survival differences. New biological agents (targeted therapies) as describe above might also contribute to improvement of results in future, as well as to tailored therapy based on the molecular profile of both the tumor and the patient.

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