



Efficacy Of Neo-Adjuvant Chemotherapy For The Locally Advanced Gastric Cancer: A Review Article

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ABSTRACT: Gastric carcinoma is one of the highest cancer death related disease in worldwide with the crucial 5 year survival outcome. Most of the patients are diagnosed at advanced stage on presentation and thus indicating poor outcomes. Patients who had early diagnosis are considered as a resectable disease in which surgical resection will be the potential curative treatment followed by adjuvant chemotherapy to overcome the micro metastatic lesions. For a non resectable disease, that is surgically unfit but medically fit candidates require neo-adjuvant, adjuvant or palliative treatment. Since most of the patients are diagnosed as advanced disease, these candidates are not suitable to undergo surgical resection but health related Quality of Life (QOL) need to be addressed. Many chemotherapy drugs have shown their efficacy as neo-adjuvant treatment for locally advanced gastric carcinoma. Chemotherapy works mainly by inhibiting tumor angiogenesis by blocking the action of VEGF. The most common drugs used for neo-adjuvant chemotherapy includes Cisplatin, S-1, Fluorouracil, Docetaxel, Epirubicin, Sunitinib which can be used alone or in combination with another drugs. Their efficacy as neo-adjuvant chemotherapy is briefly discussed in this review article.

KEYWORDS: Neo-adjuvant chemotherapy, Advanced Gastric Carcinoma, Response rate, Time to Progression, Survival Rate, Quality of Life.

Received 13 October, 2018; Accepted 29 October, 2018 © The author(s) 2018. Published with open access at www.questjournals.org

I. INTRODUCTION

Gastric carcinoma is a type of adenocarcinoma and is the most common primary malignant gastric neoplasm arising in the stomach. Earlier Gastric carcinoma was among top ten and now it has declined due to the upcoming research, recent development in the technologies and due to the application of neo-adjuvant chemotherapy (1). Countries like China, Japan and Eastern Asia has high incidence of gastric carcinoma, the survival rate of gastric carcinoma is poor because most of the patient have advanced disease at presentation in which the 5 year survival rate remains low that is less than 30%. Surgical resection is the only mode of curative treatment for gastric cancer in patient with no metastasis and evidence of advance disease (2, 3, 4)

Due to poor prognosis of gastric carcinoma, neo-adjuvant chemotherapy can be administered in patient with locally advanced disease (1, 2, 5). Neo-adjuvant chemotherapy before surgical resection can down-regulate the disease, therefore chemotherapy can improve the survival rate and / or can provide significant palliation of the symptoms.

Patients with gastric carcinoma can be divided into two categories: namely surgically unfit and medically fit patients. Surgically unfit patients indicate the presence of locally advanced disease and / or metastasis and presence of other contraindication. Medically fit patients include surgically unfit plus no other comorbidities and can tolerate medical therapy such as chemotherapy. Palliative chemotherapy is the main stay treatment for medically fit patients and not for the surgically unfit patients (20, 21).

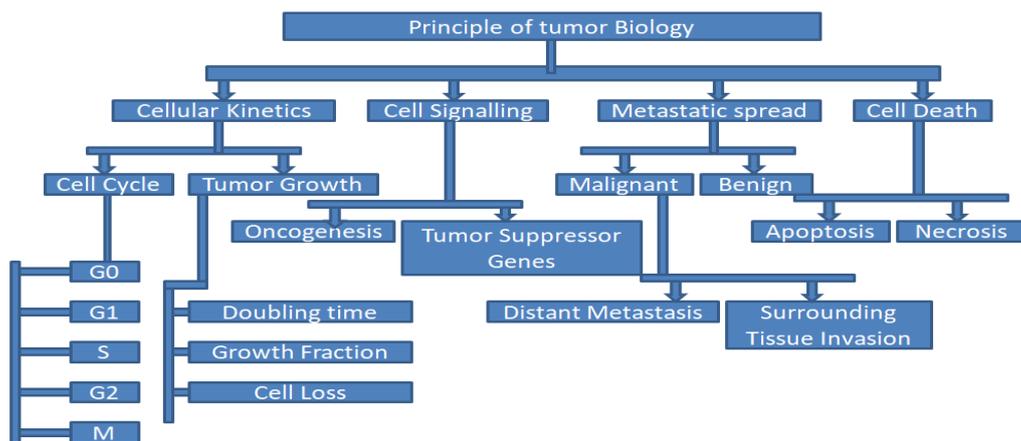
Histologically, gastric cancer is considered as aggressive tumor with high metastatic rate and the peritoneum being the commonest location with a death rate of two years once the metastasis is occurred to the

peritoneum (25, 26). In order to deal with peritoneum metastasis, chemotherapy (intraperitoneal chemotherapy) can be given pre-operatively and post-operatively, this also increases the chance of curative resection. The chemotherapy administered intraperitoneally for peritoneal metastasis for the gastric cancer has higher efficacy and lesser adverse effects as compared to the chemotherapy administered systemically (19).

The most common chemotherapeutic drugs used for the treatment of advance gastric carcinoma include Cisplatin, Docetaxel, Fluorouracil, Sunitinib, Regorafenib and S-1. These drugs can be given in combination or without combination. Docetaxel is most widely used as a second line treatment for gastric cancer, it has anti-tumor activity by inhibiting BCL2 gene and VEGF. Docetaxel mostly given in combination with Sunitinib, Cisplatin or Fluorouracil. The main disadvantage of Docetaxel is its high rate of toxicity such as Neutropenia and Neurotoxicity which leads to the discontinuation in treatment (Ilsan, 2007). Sunitinib exerts its anti-tumor activity by inhibiting tyrosine kinase that is involved in tumor proliferation and angiogenesis. S-1 is an oral Fluoropyrimidine mostly combined with Cisplatin and also can be considered as first line treatment for advanced gastric carcinoma. Cisplatin and Fluorouracil chemotherapy has been used in treatment of advanced stage of gastric carcinoma with improvement of survival outcome (27).

Mechanism Of Action Of Chemotherapeutic Drugs

The main aim of the chemotherapeutic drugs is to arrest the tumor growth by inhibiting the specific molecular targets and interfering in the cell division. Understanding the basic principle in the mechanism of action of anti-cancer drugs is significantly essential in order to master the principles of tumor biology.



The principle of tumor biology is briefly described in Figure-1.

Initially, the tumor grows at a steady rate followed by rapid doubling rate of growth and then the growth is influenced by rate of cell death and blood supply to the tumor. Therefore, chemotherapy can have a profound effect on the tumor growth (size). Tumor growth curve Figure-2 shows a sigmoid shape growth curve. Cell signaling is stimulated via external signal which is called growth factor. The process involved in cell signaling is cell cycle stimulation which includes cell division, cell migration and cell death. The process of oncogenesis is stimulated when proto-oncogenes changes from its non-mutated form to mutated form. Figure-3 below briefly summarizes the flow of oncogenesis. Metastasis occurs when the cell integrity caused by cell adhesion molecules is disturbed. The protein responsible for cell integrity is integrin, eventually the ultimate result of tissue integrity abnormalities will lead to local invasion and metastasis. In cancer the role of chemotherapy is to induce apoptosis rather than necrosis, the reason is because no inflammation is encountered and chemotherapy causes mutation of cancer cell which ultimately leading to apoptosis.

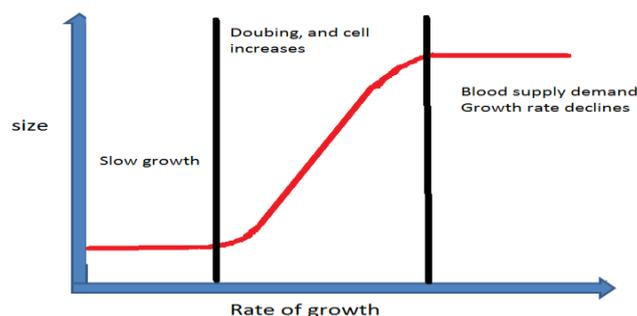


Fig. 2: Tumor Growth curve

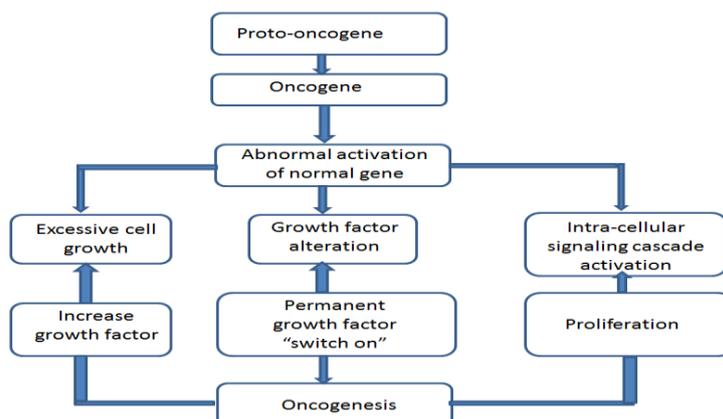


Fig.3 Flow chart of Oncogenesis

Anti-cancer therapy produces different clinical responses : Complete Response (complete resolution of tumor), Partial Response (less than 50% decrease in tumor size), Progression Response (tumor size increase greater than 25%), Stable Disease Response (between complete response and tumor progradation).The second clinical response to anti-tumor therapies is to access circulating tumor markers.

Anti-cancer drugs such as Methotrexate and Vinca-alkaloids acts on S-phase and M-phase of the cell cycle respectively by killing the proliferating cell which is achieved by DNA-synthesis inhibition and arresting M-phase of the cell cycle. As most of the chemotherapy agents acts on the actively dividing cell, chemotherapy is mostly targeting the specific phase of cell cycle. Therefore, it is understood that increased duration of exposure of chemotherapy drugs is better than increasing the drug dose. The main different between cell cycle specific chemotherapy and cell cycle non-specific chemotherapy is that increased dose is required in the latter than former.

Alkylating agent such as Melphalan, Chlorambucil, and Cyclophosphamide reacts with DNA and interfere with the enzymatic action involved in DNA replication. The ultimate result of alkylating agent is causing the cell to undergo apoptosis and hence, the phase were alkylating agent act is on the S-phase of cell-cycle (DNA synthesis inhibition). Platinum agents such as Cisplatin, Oxaliplatin etc inhibit DNA, RNA, and protein synthesis.

Anti-metabolites are group of drugs that require continuous treatment because of their exertion over a longer period of time. The main action of anti-metabolites is DNA, RNA synthesis inhibition and examples include Methotrexate, Fluorouracil, Cytarabine and Gemcitabine. Cytotoxic antibiotics prevent transcription activity during DNA synthesis which leads to apoptosis of the cell and DNA fragmentation. Examples of Cytotoxic antibiotics include Actinomycin, Bleomycin, Mitomycin, Vinca alkaloids and Taxoids are mitotic spindle poison which disturbs the mitotic activity during cell proliferation. Topoisomerase and helicase is an enzyme that is required to unwind the DNA during the transcription process and hence, topoisomerase inhibitor is a group of drugs that inhibits transcription process during the DNA synthesis and as a result, the S-phase of the cell cycle is arrested and further DNA doubling is prevented.

Role Of Neo-Adjuvant Chemotherapy On Resectability In Locally Advanced Disease

In a study, Yu Hang Li et al, 2015 (24) evaluation of the safety and efficacy of S-1 plus Cisplatin verses 5-FU plus Cisplatin in patient with Advanced Gastric Carcinoma (AGC), their primary end point was Time To Progression (TTP) compared between two groups and found that the result obtained was not statistically significant ($P=0.859$) between the two groups. Their secondary outcome was Overall Survival (OS) which was also not statistically significant between the two groups. With regards to TTP and OS, S-1 and Fluorouracil when combined with Cisplatin, the treatment of advanced gastric cancer showed that both the group had comparable treatment efficacy (22, 23). Therefore, as per the study conducted by Yu Hang Li et al (24), S-1 can be an alternative option for continuous infusion of Fluorouracil.

In the study conducted by Pavlakis et al, 2016 (28) elaborated the efficacy of Regorafenib in targeting the tumor angiogenesis in patients with advanced gastric cancer and concluded that Regorafenib was statistically significant and effective in prolonging the progression free survival when compared with Placebo ($P<0.001$).

In a research article conducted by S.Hashemzadeh et al, 2014 (29) have evaluated the efficacy of neo-adjuvant chemotherapy in resectable patient with locally advanced gastric carcinoma and because of the upcoming researches and developed technologies, the incidence of gastric carcinoma can be declined with the application of neo-adjuvant chemotherapy (1). Their research study showed statistically significant result on resectability of locally advanced gastric carcinoma with the administration of neo-adjuvant chemotherapy

($P < 0.05$) whereas age and gender did not show any significant result with the administration of the neo adjuvant chemotherapy.

The only known and potential mode of curative treatment in patient with gastric cancer with no evidence of metastasis is surgical resection (2, 3, 4) but neo-adjuvant chemotherapy is reserved for patient with resectable tumor and patient with micro-metastatic lesion. Neo-adjuvant chemotherapy can improve the patient's survival rate (5). Chemotherapy followed by CT is required to access the disease status (6, 7). Oki et al, conducted in his study that Docetaxel plus S-1 is effective for the resectability of locally advanced gastric cancer (8) which is in accordance with S.Hashemzadeh et al, 2014(29). Del Rio et al, also concluded that preoperative chemotherapy is useful in advanced gastric cancer and also suitable for young patients (9). Nagahama et al, proposed that neo adjuvant chemotherapy can regress the tumor in patient with advanced gastric cancer treated with S-1 and Cisplatin (10). Neo-adjuvant chemotherapy can also increase the survival rate as reported by Lowy et al.

In a study conducted by JH Yi et al, 2012 (30), second line chemotherapy with Docetaxel is considered as better than the supportive care therapy in patients with advanced disease (metastatic disease) because clinical studies have been only conducted which showed the importance of disease progression in patients taking second line chemotherapy compared to patients taking supportive care therapy ($P = 0.004$)

The efficacy of the Docetaxel, Cisplatin and Fluorouracil has been studied in an article published by Chen et al, 2013 (32) which showed that Docetaxel, Cisplatin and Fluorouracil has better response in time of partial response of the tumor size preoperatively ($P = 0.0003$) and decreased progression of the disease ($P = 0.0005$) as compared to the patients who did not receive Taxane containing palliative chemotherapy for advanced gastric cancer, it is also stated that palliative chemotherapy can be administered in patients who are surgically unfit but medically fit (20,21).

Gastric cancer usually does not metastasize to the distant organ until the third stage, but it can metastasize to the lymph node during the early stage, which is an important prognostic factor. The tumor marker CA 19-9 maybe associated with the metastasis and with the advance in the gastric cancer ($P = 0.08$) (16) distant metastasis is not commonly seen in gastric cancer were as local metastasis (lymph node) is the early finding as well as it contributes in the evaluation of the cancer prognosis. The depth of cancer and number of the metastatic lymph node are the most important prognostic factor for curative gastric cancer surgery. The common location for gastric cancer to metastasize is peritoneum which eventually decreases the five year survival to less than two years due to development of peritoneal carcinomatosis (17, 18). The chemotherapy administered intraperitoneally for peritoneal metastasis from the gastric cancer has higher efficacy and lesser side effect as compared to chemotherapy administered systematically (19). The baseline characteristics of the included articles to draft this manuscript is briefly summarized in table given below.

Table: Baseline characteristics of the included studies.

Study ID	Design	Intervention	Outcomes	Results
YuHong Li et al, 2015 (24)	RCT	S-1 + Cisplatin VS 5 FU + cisplatin	TTP OS	NS ($P = 0.859$) NS ($P = 0.820$)
Pavlakis et al, 2016 (28)	RCT	Regorafenib VS Placebo	Progression to survival	S ($P < 0.001$)
S.Hashemzadeh et al, 2014 (29)	RCT	Neo-adjuvant chemo VS Surgery in AGC	Resectability Age Gender	S ($P < 0.05$) NS ($P > 0.05$) NS ($P > 0.05$)
JH Yi et al, 2012 (30)	RCT	Docetaxel+ Sunitinib In patient previously treated 5-FU + Platinum	TTP RR	NS ($P = 0.206$) S ($P = 0.02$)
Sadighi et al, 2006 (31)	RCT	Docetaxel, Cisplatin, 5-FU VS Epirubicin, cisplatin, 5-FU	RR QOL Survival	NS ($P = 0.69$) S ($P = 0.001$) NS ($P > 0.05$)
Chen et al, 2013 (32)	RCT	Docetaxel, cisplatin, 5-FU VS Non taxane	Partial RR Disease progression 2 year survival 1 year survival TTP	S ($P = 0.0003$) S ($P = 0.0005$) S ($P = 0.0006$) NS ($P = 0.08$) NS ($P = 0.49$)

RCT: Randomized Controlled Trial, 5-FU: Fluorouracil, TTP: Time to Progression, OS: Overall Survival, QOL: Quality of Life, RR: Response Rate, S: Significant, NS: Non-Significant

Role Of Chemotherapy In Quality Of Life Improvement

Chemotherapy not only is focused on the health issues but also on the quality of life. Quality of life (QOL) is one of the important factors which must be considered in patients with advanced gastric cancer (12). The quality of life in advanced gastric cancer is more important than the survival outcome or other health related issues when dealing with non-curable gastric cancer. For this reason, different therapies and regime can determine the quality of life.

Quality of life assessment can give us idea whether the treatment mode could be a curative or palliative. It can be assessed by a questionnaire that measures the physical activity, role, emotional and social functional domains. Sadighi et al, 2006 (31), has performed a study on quality of life assessment on patient who received taxane group of chemotherapy and compared with the patient who did not receive a taxane consisting drugs. Their study outcome were response rate, quality of life and survival and final outcome showed that quality of life and response rate were improved significantly ($P=0.001$) but not in the survival rate ($P<0.05$) and therefore, adding a taxane such as Docetaxel to the chemotherapy regimen as mode of treatment in a patient with advanced gastric cancer can improve the quality of life and also provide adequate palliation to the patient (13, 14). In patients with gastric cancer with good performance status, first line chemotherapy improves overall survival and quality of life compared with best supportive care (15).

II. CONCLUSION

Docetaxel, Cisplatin and fluorouracil regimen for palliation can improve the survival outcomes in patients with gastric carcinoma. Patients who received Cisplatin combined with S-1 had higher adverse effects when compared with Cisplatin combined with fluorouracil in patients with advanced gastric carcinoma. Most common adverse effects encountered were nausea/vomiting, hyperbilirubinemia etc as mild adverse effects and serious adverse effects were bleeding abnormality (Pancytopenia). Increased response rate were seen when Sunitinib added to the Docetaxel regimen in patients with metastatic gastric cancer. Regorafenib can prolong progression free survival when used for the treatment of AGC. This review article hereby concludes that neo-adjuvant chemotherapy can increase tumor resectability, improve TTP and OS in patients with locally advanced gastric carcinoma.

Conflict Of Interest

The authors declare no conflict of interest.

AKNOWLEDGMENT

I would like to convey my sincere gratitude to Prof. YC Wei for encouraging me in this review article manuscript. My sincere thanks to Dr Rahmathullah M.N and Dr Sonia Ahmed in helping me reviewing it before submission.

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Safat S "Efficacy Of Neo-Adjuvant Chemotherapy For The Locally Advanced Gastric Cancer: A Review Article "Quest Journals Journal of Medical and Dental Science Research 5.5 (2018): 61-66