The Prognostic Value of the Prechemotherapy Neutrophil - Lymphocyte Ratio in Gastric Cancer

Thesis

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Monika Magdy Youssef

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List of Abbreviations

Abb.	Full term
AGC	Advanced gastric cancer
AID	Activation induced deaminase
APCs	Antigen-presenting cells
APE1	Apurinic/apyrimidinic endonuclease 1
ASIR	Age-standardized incidence rate
BMDCs	Bone marrow-derived cells
BSC	Best supportive care
CO	carbon monoxide
CRP	C-reactive protein
CRT	Chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic cells
DCR	Disease control rate
DFS	Disease-free survival
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
FAP	Familial adenomatous polyposis
FFQ	Food frequency questionnaire
GC	Gastric cancer

List of Abbreviations (Cont.)

Abb.	Full term
GEJ	Gastro-esophageal junction
HDGC	Hereditary diffuse gastric cancer
HER2	Human epithelial growth factor receptor 2
HIPEC	Hyperthermia intraperitoneal chemotherapy
JGCA	Japanese Gastric Cancer Association
JPS	Juvenile polyposis syndrome
LRRFS	Loco-regional recurrence free survival
LVI	Lympho-vascular invasion
MAPK	Mitogen-activated kinase
mGC	metastatic gastric cancer
mGPS	Modified Glasgow Prognostic Score
MHC	Major histocompatibility complex
MMP-9	Matrix metalloproteinase
NK	Natural killer cells
NKT	Natural killer T cells
NLR	Neutrophil to Lymphocyte ratio
NOC	N-nitroso compounds
OAR	Organs at risk
ORR	Objective response rate
OS	Overall survival
PAH	Polycyclic aromatic hydrocarbons
pCR	pathological complete response
PDGFR	Platelet derived growth factor receptor
PFS	Progression-free survival

List of Abbreviations (Cont.)

Abb.	Full term
PI3K	Phosphoinositide 3-kinase
PJS	Peutz-Jeghers syndrome
PLR	Platelet to lymphocyte ratio
PNI	Perineural invasion
PTEN	Phosphatas and Tensin homolog
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	Relapse free survival
ROS	Reactive oxygen species
RR	Response rate
STAT3	Signal transducers and activators of transcription
TAMs	Tumor-associated macrophages
TDSFs	Tumor-derived secreted factors
TGF-α	Transforming growth factor alpha
TGF-α	Transforming growth factor- α
TKI	Tyrosine kinase inhibitor
TNF α	Tumor necrosis factor alpha
TTP	Time to progression
VEGF	Vascular endothelial gross factor
WPT	Water pipe tobacco

INTRODUCTION

Gastric cancer is the fifth most common cancer worldwide, with about one million (952,000) new cases diagnosed annually ***(Chen et al., 2015).***

More than 70% of gastric cancers occur in developing countries, particularly in Eastern Asia. The peak age for gastric cancer is 60-80 years ***(Zeeneldin et al., 2014).***

According to the GLOBOCAN database, gastric adenocarcinoma (GC) is the third leading cause of cancer-related death worldwide, after lung and liver malignancies, resulting in around 723,000 deaths in 2012 ***(Ferlay et al., 2015).***

Although there have been advances in diagnosis and management, most GC patients present with locally advanced or metastatic disease, with a 5-year survival rate of <10% ***(Wang et al., 2015).***

In Egypt, gastric cancer is the 12th most common cancer in both sexes, representing 1.6 % of total cancers. It's the 12th leading cause of cancer death, representing 2.2 % of total cancer mortality. Median age of gastric cancer in Egypt is 56 years ***(Zeeneldin et al., 2014).***

Environmental risk factors include Helicobacter pylori (H. pylori) infection, smoking, high salt intake and other dietary factors. Though most gastric cancers are considered sporadic, it is estimated that 5 % to 10 % have a familial component; and 3 % to 5 % are associated with inherited cancer predisposition syndromes. The most common hereditary cancer predisposition syndromes are: - Hereditary Diffuse Gastric cancer, Lynch Syndrome, Juvenile Polyposis Syndrome, Peutz-Jeghers Syndrome and Familial Adenomatous Polyposis ***(NCCN Guidelines Version 1.2017).***

Treatment strategies are determined by TNM staging system. However, many patients of the same TNM stage have different prognoses ***(Jingxu Sun et al., 2015).***

Gastric Cancer exhibits diverse prognoses according to various intrinsic characteristics. Therefore, the development of efficient treatment strategies for the various prognostic groups within GC is important. With this, we can more readily understand the underlying biological mechanisms of each subtype of GC, to effectively individualize each treatment strategy ***(Chan-Young et al., 2017).***

Several prognostic factors in GC have been reported: - performance status, tumor burden, tumor markers such as carbohydrate antigen 19-9 (CA-19-9), the high metabolic landscape of the tumor and weight loss during chemotherapy. They have been independently correlated with a poor prognosis ***(Ock et al., 2016).***

It is increasingly recognised that variations within clinical outcomes in cancer patients are influenced; by not only the oncological characteristics of the tumor, but also the host-response factors. The possibility of combining multiple clinically available host- and tumor related factors is of great interest; as it might serve as an excellent basis for clinical decision-making, treatment planning and establishing follow-up schedules ***(Chen et al., 2015).***

A number of studies have focused on tumor microenvironment, which is associated with the systemic inflammatory response; and may play an important role in cancer tumorigenesis and progression ***(Jingxu Sun et al., 2015).*** This inflammatory response reflects a non-specific response to tumor hypoxia tissue injury and necrosis ***(Chua et al., 2012).***

Systemic inflammatory response to tumors increases metastasis through the inhibition of apoptosis, augmentation of angiogenesis and DNA damage ***(Aldemir et al., 2015).***

Many markers of systemic inflammation response to tumors have been investigated as prognostic and predictive biomarkers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) ***(Nozoe et al., 2011).***

Inflammatory cytokines and chemokines can be produced by both the tumor and associated host cells, such as leukocytes, and contribute to malignant progression**.**

Neutrophilia, as an inflammatory response, inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells and natural killer cells.

Neutrophils and other cells, such as macrophages, have been reported to secrete tumor growth promoting factors, including: - vascular endothelial growth factor, hepatocyte growth factor, IL-6, IL-8, matrix metalloproteinases and elastases. Thus, they likely contribute to a stimulating tumor microenvironment ***(Templeton et al., 2014).***

The importance of lymphocytes has been highlighted in several studies; in which increasing infiltration of tumors with lymphocytes has been associated with better response to cytotoxic treatment and prognosis in cancer patients ***(Loi et al., 2013).***

The neutrophil to lymphocyte ratio (NLR), which is suggested as the balance between pro-tumor inflammatory status and anti-tumor immune status, has been shown to be associated with outcomes in patients with various types of malignancies ***(Pistelli et al., 2015)*** such as Renal cell carcinoma, Hepatocellular carcinoma and colorectal cancer ***(Pichler et al., 2013).***