Utility of Serum Galactomanann Monitoring in Predicting Response to Empiric Antifungal therapy in Neutropenic Patients Following Intensive Chemotherapy

Thesis

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List of Abbreviations

Abbreviation	
5-FC	5- fluorocytosine
5-FU	5-fluorouridine
ABCD	Amphotericin B colloidal dispersion
ABLC	Amphotericin B lipid complex
AGIHO	ArbeitsgemeinschaftInfektionen in der Hämatologie und Onkologie
AIDs	acquired immune deficiency syndrome
ALL	acute lymphoblastic leukemia
AmB	Amphotericin B
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCO	The American Society of Clinical Oncology
b.i.d	two times a day
BAL	Broncho Alveolar Lavage
BG	b-D-glucans
BMT	bone marrow transplant
BUN	blood urea nitrogen
CBC	complete blood picture
CHF	congestive heart failure
CHOP	cyclophosphamide, oncovin , hydroxydaunorubicin, prednisolone

List of Abbreviations (Cont.)

Abbreviation	
CNS	central nervous system
CrCl	creatinine clearance
CSF	cerebro spinal fluid
CSF	cerebrospinal fluid
CSFs	Colony-stimulating factors
CT	computed tomography
CYP	cytochrome P
D-AmB	Amphotericin B deoxycholate
DNA	deoxyribo nucleic acid
EAPCRI	The European Aspergillus PCR Initiative
ELISA	enzyme-linked immunosorbent assay
EORTC/MSG	European Organization for Research and Treatment of Cancer/Mycoses Study Group
ESBL	Extended Spectrum Beta Lactamase
FDA	food and drug administration
FDG	Fluorine 18 fluorodeoxyglucose
FN	febrile neutropenia
GFR	glomerulus filtration rate
GI	gastro intestinal
GM	galactomannan

List of Abbreviations (Cont.)

Abbreviation	
GM-CSF	granulocyte- macrophage colony stimulating factor
H.Capsulatum	HistoplasmaCapsulatum
Hb	Haemoglobin
HIV	human immune deficiency virus
HP-βCD	Hydroxypropyl-β-cyclodextrin
HRCT	Highresolution computed tomography
HSC	hepatosplenic candidosis
HSCT	hematopoietic stem cell transplant
HSV	Herpes Simplex Virus
IDSA	Infectious Diseases Society of America
IFD	Invasive fungal disease
IV	intra venous
L-AmB	Liposomal amphotericin B
MASCC	Multinational Association for Supportive Care in Cancer
MDS	myelodysplastic syndrome
MIC	minimun inhibitory concentrations
MRI	magnetic resonance imaging
MRSA	Methicillin Resistant Staphylococcus Aureus
NCCN	National Comprehensive Cancer Network

List of Abbreviations (Cont.)

Abbreviation	

NPV ..... negative predictive value

OATP ..... organic anion transport proteins

PATH ..... Prospective Antifungal Therapy

PBSC ..... peripheral blood stem cell

PCR ..... polymerace chain reaction

PET ..... positron emission tomography

po ..... per oral

PVV ..... positive predictive value

rG-CSF ..... recombinant human granulocyte colony stimulating factor,

rRNA ..... ribosomal ribo nucleic acid

SBECD ..... sulfobutylether-β-cyclodextrin

SC ..... subcutaneous

SE-βCD ..... sulfobutyl ether β-cyclodextrin

T.L.C ..... Total lecocytic count

TMP-SMX ..... Trimethoprim/sulfamethoxazole

TRANSNET ..... The Transplant-Associated Infections Surveillance Network

UGT ..... uridinediphosphate glucuronosyl transferase

VRSE ..... Vancomycin-Resistant Staphylococcus epidermidis

WBC ..... White bolod cell

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Introduction

Introduction

Neutropenia is defined as a neutrophil count of less than 500 cells per mm^3, or a neutrophil count of less than 1000 cells per mm^3, with a predicted decrease to less than 500 cells per mm^3. ***Hughes Wt., et al. 2002.***

Chemotherapy induced neutropenia (CIN) is the most serious hematologic toxicity of cancer chemotherapy – ***Crawford J, et al., 2004.***

CIN predispose patients with cancer to life threatening infection particularly from gram negative bacilli, gram positive cocci and fungi by suppression of neutrophil production and by cytotoxic effects on alimentary tract.

The duration of CIN typically is 7 to 10 days. The severity and duration of a neutropenia episode with the presence of fever or febrile neutropenia increase the risk of further infection and of infection related mortality. -Caggiano V, 2005.

Despite advances in antimicrobial therapy and supportive care, invasive fungal infection remains a major clinical problem among patients with hematologic malignancies. Not only are fungal infections increasing in frequency in this patient population-, but they also are occurring earlier during the course of cytotoxic chemotherapy. The most common fungal infection is *aspergillus* 73%, candida 13%, and mucor 14% ***Groll AH, Shah PM et al., 1996.***

Mortality from aspergillosis is variable but may be as high as 90 % despite therapy - ***Richardson MD, et al., 1998.***

Although gold diagnostic standards for aspergillosis exist, they usually require invasive procedures to obtain specimens for histological examination and culture ***Walsh TJ, et al., 1994.***

Unfortunately, such aggressive procedures are often precluded by cytopenia or by the critical condition of these patients. Hence, definite diagnosis is infrequently established before death or before fungal proliferation becomes overwhelming and therapy may no longer be successful - ***Groll AH, et al., 1996.***

Newer diagnostic approaches have focused on the detection of surrogate markers such as circulating fungal antigens or metabolites. - ***Roger TR, et al., 1990.***

One such component is galactomannan (GM), a major aspergillar cell-wall constituent released during invasive disease.

Now a commercially available sandwich enzyme linked immunosorbent assay (ELISA) for the detection of GM was introduced - ***Maertens J, et al., 1999.***

The assay employs the rat monoclonal antibody EB-A2 and recognizes the 135-b-D-galactofuranoside side chains of the GM molecule. By using the same antibody as both capture and detector antibody.

Also the cut off level is now world-wide lowered to 0.5 which will help to further standardize and compare this diagnostic tool ***Stynen D, et al., 1995.***

Circulating galactomannan may be detected at a median of5–8 days (range, 1–27 days) before clinical signs and symptomsof invasive aspergillosis become evident - ***Maertens J, et al., 2001.***

Furthermore, the concentration of circulating galactomannan corresponds with the fungal tissue burden Patterson TF, et al 1998 and may therefore be used to monitor the patient's response to antifungal treatment - ***Verweij PE, et al., 1997.***