شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

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Addition of Clarithromycin in Multiple Myeloma Patients as impact of outcome and management

Thesis is
Submitted for Partial Fulfillment of Master Degree
in Internal Medicine
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Introduction

Multiple myeloma (MM) accounts for 1.6% of all cancers and 5% to 10% of all hematologic malignancies (Anwer et al., 2018).

It is considered a treatable but incurable disease, and thus lifelong observation and follow- up are recommended (Anderson et al, 2016). International Myeloma Working Group updated indications to start treatment in MM patients. Some laboratory and radiographic variables are added to existing CRAB features. These features include bone marrow plasma cells ≥60%, abnormal MRI with more than one focal lesion, with each lesion >5 mm, and involved/uninvolved serum free light chain ratio ≥100 (Rajkumar, 2016).

The macrolide family of antibiotics is widely used for bacterial infections and especially those produced by Mycoplasmas and atypical bacteria. (Azuma et al.,2014).

Among macrolides, clarithromycin (CLA) has higher stability under acidic environments making it suitable for oral delivery (Mordi et al.,2000).
It is effective against C. pneumonia,

M. pneumomiae, P. aeruginosa, K. pneumonia, S. pneumonia, S. aureus, H. influenza, B. pertussis, Legionella and Campylobacter responsible for respiratory tract infections as well as H. pylori responsible for peptic ulcer (Nagata et al.,2004)

There is evidence that clarithromycin is a potent and continuous inhibitor of autophagy in both myeloma and chronic myeloid leukaemia cells.
(Nakamura et al.,2010)

The combination of clarithromycin and bortezomib resulted in increased cytotoxicity compared to bortezomib alone . (Marixa et al.,2013)

Aim of the Work

The aim of the study is to determine the benefits and risk of adding clarithromycin as standard regimen in multiple myeloma patients whether denovo or refractory pre bone marrow transplntation and its effect on remission rates and survival rates in Multiple myeloma patients.

Chapter one
Multiple myeloma

Definition:

Plasma cell dyscrasias encompass a spectrum of disease which include asymptomatic premalignant proliferation of plasma cells (monoclonal gammopathy of unknown significance [MGUS]) and asymptomatic MM (smoldering MM (SMM)) to malignant disease (MM and plasma cell leukemia) with end-organ damage and associated significant patient morbidity (Landgren et al.,2013).

Multiple myeloma is known as uncontrolled proliferation of monoclonal plasma cells in the bone marrow, leading to production of nonfunctional intact immunoglobulins or immunoglobulin chains (Swerdlow et al.,2008).

It is considered a treatable but incurable disease, and thus lifelong observation and follow- up are recommended (NCCN guidelines.,2016).

Incidence:

Multiple myeloma (MM) is the second most commonly diagnosed hematological neoplasm, with an incidence rate of 6.2 per 100 000 individuals (Seigel et al.,2016). It accounts for 1.6% of all cancers and 5% to 10% of all hematologic malignancies (Anwer et al.,2018). It accounts for 10%–15% of all lymphohematopoietic cancers (LHCs) , 27% of all LHC deaths, and 0.9%–2% of all cancer-related mortalities(Mahindra et al.,2010).

Risk factors:

1-Age:
Myeloma is strongly related to age, with the highest incidence rates being in older people. In the UK in 2013-2015, on average each year almost half (45%) of new cases were in people aged 75 and over (WCISU Wales.2017).

2-Gender:
Incidence rates are significantly higher in males than females in a number of (mainly older) age groups. The gap is widest at age 90+, when the age-specific

incidence rate is 2 times higher in males than females (WCISU Wales.2017).

3-Race:
Age-sstandardise rates for White males with myeloma range from 6.1 to 6.5 per 100,000. Rates for Asian males are similar, ranging from 3.6 to 6.4 per 100,000, whereas the rates for Black males are significantly higher, ranging from 10.9 to 18.2 per 100,000. For females there is a similar pattern - the age-standardised rates for White females range from 3.9 to 4.2 per 100,000. Rates for Asian females are similar, ranging from 2.3 to 4.4 per 100,000, whereas the rates for Black females are significantly higher, ranging from 6.6 to 11.5 per 100,000. (NCNN guidelines .,2009).

A similar ethnic pattern has been observed in the UK for almost 40 years, with myeloma occurring around twice as frequently in African Americans as Caucasians (Howlader et al.,2011)

It appears that, in comparison with white people, black people have younger myeloma onset (Waxman et al.,2010)

4 -Body mass index(BMI):
Obesity is known as attributable factor for M.M (Brown.et al.,2018).

Myeloma risk is 12% higher per 5-unit body mass index (BMI) increment, a meta-analysis showed (Wallin et al.,2011) . However, the association may be limited to males (Xue et al.,2017).

Obese people may produce more of the protein interleukin-6 (IL-6), affecting proliferation and development of normal and malignant plasma cells (Larsson et al.,2007).

5 -Familial risk :
Myeloma risk is 2.3 times higher in people with a firstdegree relative (parent, sibling or child) with myeloma compared with the general population, a cohort study showed (Frank et al.,2014).

6 -Anticedental medical contions :
Myeloma risk is 50% higher in people with pernicious anaemia, versus those without the disease, a systematic review showed that Monoclonal gammopathy of undetermined significance (MGUS) - a precursor for myeloma risk is 67% higher in people with pernicious anaemia (McShane et al.,2014).

7 -Occupational risk: several studies have reported associations between MM and occupations that may entail exposure to chlorinated solvents, including chemical work, (Greenberg et al.,2001) construction work,(Mester et al.,2006) painting,(Lundberg et al.,1998) metal work,(Lope et al.,2008) farm work,

(Svec et al.,2005) and hairdressing (Miligi et al.,1999) .

Diagnosis:

The key clinical and laboratory features in Myeloma are :

Anemia <12 g/100 m , Bone lesions (lytic lesions, pathologic fractures or severe osteopenia) , Renal failure (serum creatinine ≥2mg/100 ml) , Hypercalcemia (≥11 mg/100 ml) , Monoclonalgammopathy on serum protein electrophoresis , Monoclonal protein on serum protein immunofixation (93%) , Monoclonal protein on serum plusurine protein immunofixation (or serum immunofixation plus serum free light chain assay) , Type of M protein : IgG (52%) , IgA (21%) ,Light chain only (16%) , Increased ≥10% clonal bone marrow plasma cells (96%) (Kyle et al.,2003) .

In 2014, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for MM and Plasma Cell related disorders (Rajkumar et al.,2014) :

Disorder	Disease Definition
Non-IgM monoclonal gammopathy of undetermined significance (MGUS)	All 3 criteria must be met: 1.Serum monoclonal protein (non-IgM type) <3gm/dL 2.Clonal bone marrow plasma cells <10%*
	3.Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder
Smoldering multiple myeloma	Both criteria must be met: 1.Serum monoclonal protein (IgG or IgA) ≥3gm/dL, or urinary monoclonal protein ≥500 mg per 24h and/or clonal bone marrow plasma cells 10–60% 2.Absence of myeloma defining events or amylodosis.

Multiple Myeloma	Both criteria must be met: 1.Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma 2.Any one or more of the following myeloma defining events: A- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
	▪ Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) ▪ Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 μmol/L (>2 mg/dL) ▪ Anemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a hemoglobin value <10

	g/dL ▪ Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT) B- Clonal bone marrow plasma cell percentage ≥60%) C- Involved: uninvolved serum free light chain (FLC) ratio ≥100 (involved free light chain level must be ≥100 mg/L)) D- >1 focal lesions on magnetic
	resonance imaging (MRI) studies (at least 5mm in size)