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Hematological and Biochemical Changes in Patients with Multiple Myeloma Treated with Bortezomib Based Triple Drug Combination Chemotherapy

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Abstract **Background:** Multiple Myeloma (MM) is a neoplastic clonal disorder and accounts for 1% of malignant tumors and 10%–15% of hematopoietic neoplasms. The prognosis of Multiple Myeloma has reversed by the advent of novel agents and triple combination therapy (Bortezomib, Thalidomide, Dexamethasone) that serve the basis of future strands of care in Multiple Myeloma patients. **Objective:** The aim of the study was to assess the safety, efficacy and tolerability of Bortezomib in newly diagnosed cases of Multiple Myeloma patients in Bangladesh. **Materials &Methods:** We undertook this clinicopathological study to assess the profile of Multiple Myeloma patients, evaluate hematological and biochemical response of 36 newly diagnosed cases of MM with or without renal impairment receiving 4 cycles of Bortezomib, Thalidomide and Dexamethasone (BTD). **Results:** Among the study population, 36(100%) patients had weakness. followed by anaemia (97%), bone pain (89%) and renal impairment (44%). During treatment, 8 patients (22%) suffered from somnolence, 5 patients (14%) had Peripheral neuropathy and 6 (17%) patients complained of constipation. We found 8% suffered from hyperglycaemia, 3% rash, 3% cardiac arrest, 6% electrolyte imbalance and life threatening intracranial haemorrhage occurred in 1 patient (3%). Out of 36 patients, complete response achieved in 18 patients (50%), where 6 patients (16%) showed partial response, 10 (28%) showed very good partial response and 2 (6%) patients showed no response. The overall response rate was 94% belonged to complete response(CR), Partial response(PR),very good partial response(VGPR). **Conclusion:** Bortezomib based combination therapy is a highly effective and safe regimen for newly diagnosed Multiple Myeloma patients. . It can be administered safely in the outpatient setting provided by clinicians.

Keywords: *multiple myeloma, BTD, M protein*

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1. Introduction

Multiple Myeloma (MM) is a malignant proliferation of plasma cells, associated with an M (monoclonal) protein in serum and/or urine and evidence of organ damage related to the plasma cell neoplasm [1,2,3,4]. Study of hematological malignancy in Bangladesh has evidenced that the incidence of Multiple Myeloma is 10.5%, median age 55years [1-6]. The survival ranges from few months to more than 10 years with the availability of novel agents such as thalidomide, lenalidomide, and bortezomib over recent years. [1-7,9,13,19] The clinical manifestation of Myeloma are heterogeneous and include symptoms of impaired haemopoiesis, hyperviscosity, renal dysfunction, infection, peripheral neuropathy, bone complications and extra medullary disease.Myeloma seems to be more common in men than women. [1-11,13-19] The etiology of the disease is unknown but it is more common in certain racial groups such as those of Afro-Caribbean origin [2].

Diagnostic workup may reveal a normochromic normocytic or macrocytic anaemia, marked rouleaux formation, neutropenia and thrombocytopenia in advanced disease, high C-reactive protein(CRP), and ESR, monoclonal protein in serum or urine or both, increased abnormal plasma cell > 20% in the bone marrow, hypercalcemia, hyperuricemia, low serum albumin, renal impairment, etc. Serum β2 microglobulin is often raised and is a useful indicator of prognosis. Sensitivity to drugs and clinical course vary widely among patients [5-13].

Bortezomib is a first in class proteasome inhibitor, induces growth arrest and apoptosis and reverse chemo-resistance in Myeloma cell and has demonstrated no irreversible adverse effect on Haemopoietic stem cell [1-7,9-11,13]. Bortezomib is usually given as a short intravenous infusion on days 1,4,8,11 of a 3 weekly cycle on indoor or an outpatient basis. but it is used as induction agent for its effectiveness and clinical trial results. The 72 hours gap between infusion is important to allow recovery of the proteasome inhibition in the normal cell. The ten day treatment free period allows cell recovery and prevents excessive side-effect. [25-28]

A team work with multimodality approach is often needed for successful outcome particularly in a resource poor setting. In view of insufficient data on Bangladeshi myeloma patients, we undertook this clinicopathological study to observe hematological, biochemical changes in patients of newly diagnosed Multiple Myeloma treated with Bortezomib, Thalidomide, Dexamethasone (BTD). [25]

2. Materials and Method

A prospective observational study was conducted over the period of 18 months from June 2018 to December 2019 in Bangabandhu Sheikh Mujib Medical University. Actual sample size was 36 newly diagnosed case of Multiple Myeloma. Fulfilling the criteria for entry into the study detailed clinical history, physical examinations & relevant investigations were recorded in data sheet. After taking written informed consent, these patients were enrolled in this study.

2.1. Inclusion Criteria

- Patient age >18 years,
- Newly diagnosed Multiple Myeloma
- Platelet count=100x $10^{\Lambda}9$/ L
- Absolute Neutrophil count = lxl$0^{\Lambda}9$/L
- Corrected Serum Calcium = 14mg/dl
- Serum Hepatic Amino Transferase level =2.5 x the upper limit of normal. Normal value- 7-56u/dl of serum
- Total Bilirubin =1.5 x upper limit of normal. Normal value- 0.2-1.2mg/dl and Creatinine clearance = 30ml/min.
- Patient willingly given informed consent to take part in this study.

2.2. Exclusion Criteria

- Patient or attendant unwillingly to give informed consent to take part in this study
- HIV positivity
- Age > 75 years of newly diagnosed case of Multiple Myeloma
- Relapsed or refractory Multiple Myeloma patient
- Confirmed Amyloidosis.
- History of other malignancy, uncontrolled Diabetes, Grade=2 Peripheral Neuropathy (National Cancer Institute)

All our patients were evaluated with detailed history, general and systemic examinations, hematological and biochemical parameters, bone marrow study, serum protein electrophoresis and immunofixation, estimation of serum free light chains (FLC) ratio, urine analysis and 24 hour urinary protein estimation. Data were collected using a preformed data collection sheet (questionnaire) according to the above mentioned criteria. After fulfilling the criteria for entry into this study patients were treated with inj. Bortezomib(1.3mg/m^2)as an intravenous bolus on days 1,4,8,11 in a three week cycle(twice weekly administration) in indoor and some patients as day care basis in outpatients department. Dexamethasone at 40mg was given intravenously or orally on the day of and day after inj Bortezomib.Thalidomide was given orally 50-200 mg at bedtime on days 1-21. .Each cycle was of 3 weeks duration. Anti-platelet drug (to prevent the risk of thromboembolism),antibiotic (for infection) and red cell concentrate transfusion (if hemoglobin less than 8gm/dl) were given as necessary. Most of the patients received variable number of zolendronic acid with each cycle of Bortezomib and dexamethasone, Thalidomide.(BTD)

Follow-up Time-

Indicates time between initiation of BTD Protocol and the date of last follow-up.

Follow-up Schedule-

Every 21 days interval for 6 months

Assessment Of Response:

S.protein electophoresis and bone marrow examination were done after 4 cycles of Bortezomib and Thalidomide, Dexamethasone for final assessment of responses with the following criteria. In this study we used international Myeloma working Group (IMWG) criteria to assess the response to anti-myeloma.

Response To Therapy- Indicate

- Complete response (CR)
- Partial response (PR)
- Very good partial response(VGPR)
- Non- responder (NR)

Complete response was defined as absence of M protein in serum or urine protein electrophoresis, the absence of plasmacytoma and <5% plasma cells in the bone marrow.

Partial response was defined as >50% reduction of plasma cells in bone marrow and absence of M protein in the serum and absence of urinary Bence jones protein.

Very good partial response (VGPR) was defined as ≥ 90% decrease in serum M- protein.

No-response was defined as <50% reduction of plasma cells in the bone marrow or presence of M protein in the serum or presence of urinary Bence jones protein.

Time To Obtain Response:

Indicates time between the initiation of Bortezomib, Thalidomide, Dexamethasone (BTD) and the date of completion of 4 cycles BTD therapy.

Statistical Analysis

Data were analyzed using the Package for the Social Science (version 20). A total 36 new diagnosed

patients of Multiple Myeloma were taken for induction therapy with BTD. Base data were recorded before treatment and follow up were recorded at 6 and 12 weeks.

3. Results

36 adult Multiple Myeloma patients mean age was 58.04 (SD±7.45) and median was 56. 25 patients (70%) were male and 11(30%) were female.The male to female ratio was 2.3:1.

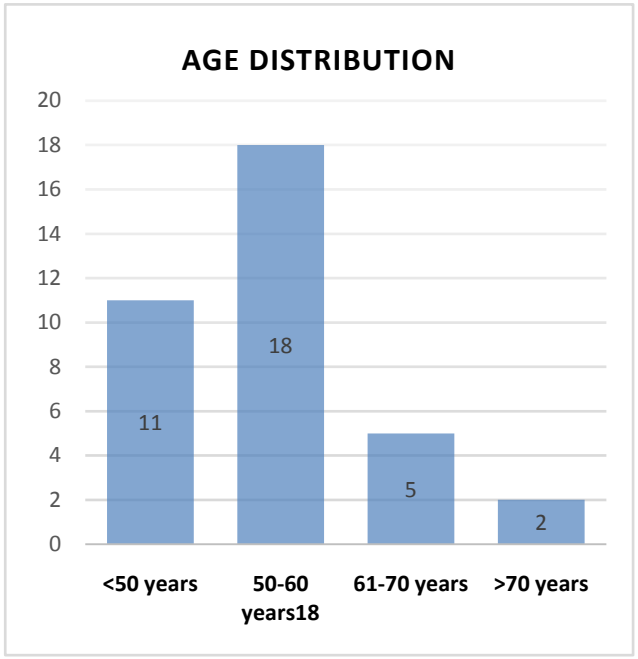

Figure 1. Bar Diagram Showing Age Distribution Of Study Patients.

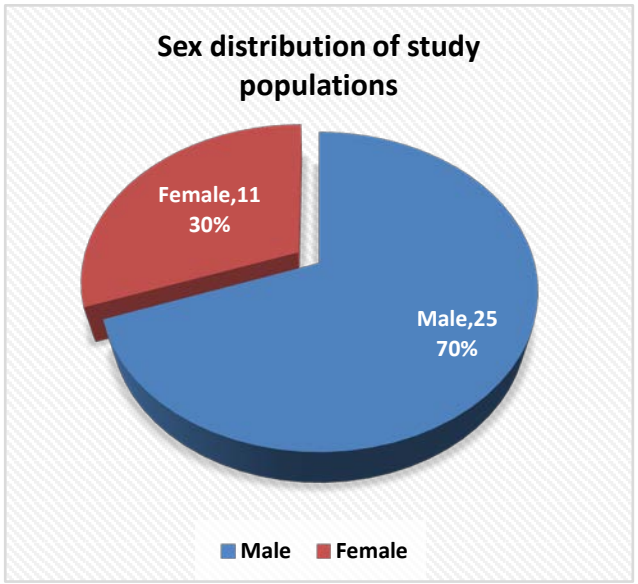

Figure 2. Pie Chart Showing Sex Distribution Of The Study Patients.

Most of the patients were businessmen (33%), other frequent occupation was service holder (28%), house wife (20%), farmer & teacher were 8% each. and doctor (3%).

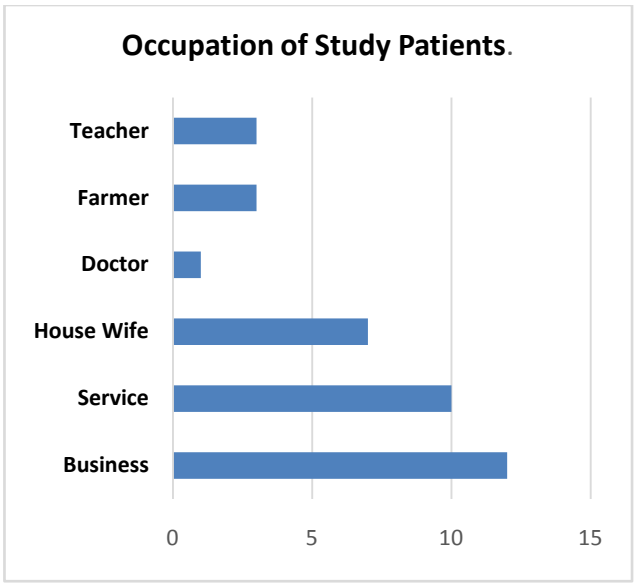

Figure 3. Bar Chart Showing Occupation Distribution Of The Study Patients

Among the study population, 97% of patients had anaemia followed by bone pain (89%) and renal impairment (44%).

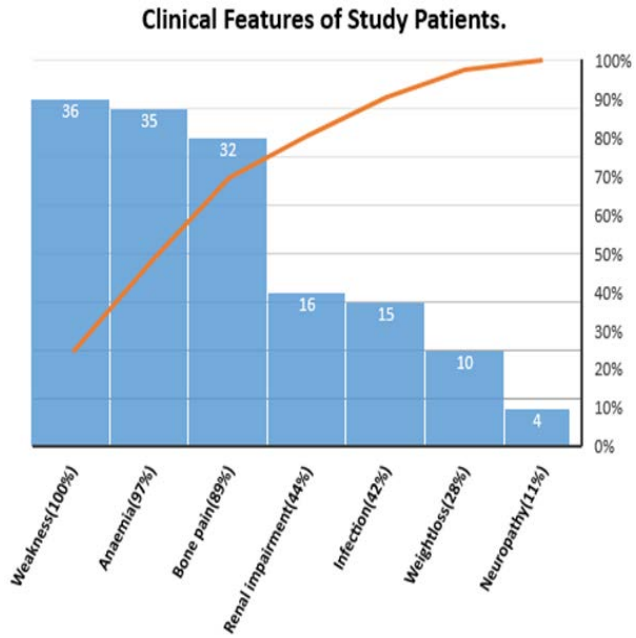

Figure 4. Bar Chart Showing Clinical Signs And Symptoms Of Study Patients.

Before treatment, mean Hb concentration was only 8.5 g/dl which was increase to 10.57g/dl and 11.84g/dl at 6 and 12 weeks**.** At diagnosis, mean of S. creatinine, S. albumin, S. calcium and β2 microglobulin were 2.5mg/dl,28.12g/L, 9.65mg/dl& 4.55mg/L respectively. At 6 weeks mean S. creatinine, S. albumin, S. calcium and β2 microglobulin were 1.64mg/dl,31.24g/L, 9.32mg/dl& 3.52mg/L respectively But at 12 weeks mean were 1.45mg/dl, 34.36g/L, 9.10 mg/dl& 2.6mg/L respectively. Mean ESR before chemotherapy was 94.76mm in Ist hour, where after treatment at 6 weeks and 12 weeks were 32 and 17.30 mm in Ist hour respectively.

Table 1. Blood/Biochemical Profile Before And After Bortezomib, Thalidomide, Dexamethasone(n=36)

Parameter (Mean Value)	Before regime	6 weeks after regime (2 cycles)	12 weeks after regime (4 cycles)
Haemoglobin(gm/dl)	8.5	10.57	11.84
TLC(thousaunds/µl)	8.5	10.11	11.23
Platelets (Lacs/µL)	2.55	2.10	1.81
ESR (mm in1st hour)	94.76	32	17.30
S.Creatinine(mg/dl)	2.5	1.64	1.45
S.Albumin(g/L)	28.12	31.24	34.36
S.Calcium(mg/dl)	9.65	9.32	9.10
B2 microglobulin(mg/L)	4.55	3.52	2.6
LDH(IU/L)	213	193	152
Bone marrow plasma	69	_	11
Cell (%)			
S.M protein (%)	78	46	13

28 patients (78%) had serum monoclonal protein (M protein). It is reduced to 46% at 6 weeks and 13% at 12 weeks of treatment. Only one patient (3%) had urinary Bence Jones protein which remained positive at 6 weeks but disappeared at 12 weeks of treatment. We found only 6 cases (16%) had bony lesion in skull and chest. Lytic lesion with fracture in spine was found in 1 case (3%).

During treatment, 8 patients (22%) suffered from somnolence and 7 patients (19%) had Peripheral neuropathy and 6 (17%) patients complained of constipation. We found 8% of suffered from hyperglycaemia, 3% rash, 3% cardiac arrest and 6% electrolyte imbalance and life threatening intracranial haemorrhage occurred in one patients (3%).

Complete response achieved in 18 patients (50%), where 6(16%), 10(28%) and 2(6%) patients belonged to partial, very good partial and no response respectively. The overall response rate was 94%.

Death occurred in 2 cases (6%), 1 patient due to intracranial haemorrhage and another from cardiac arrest.

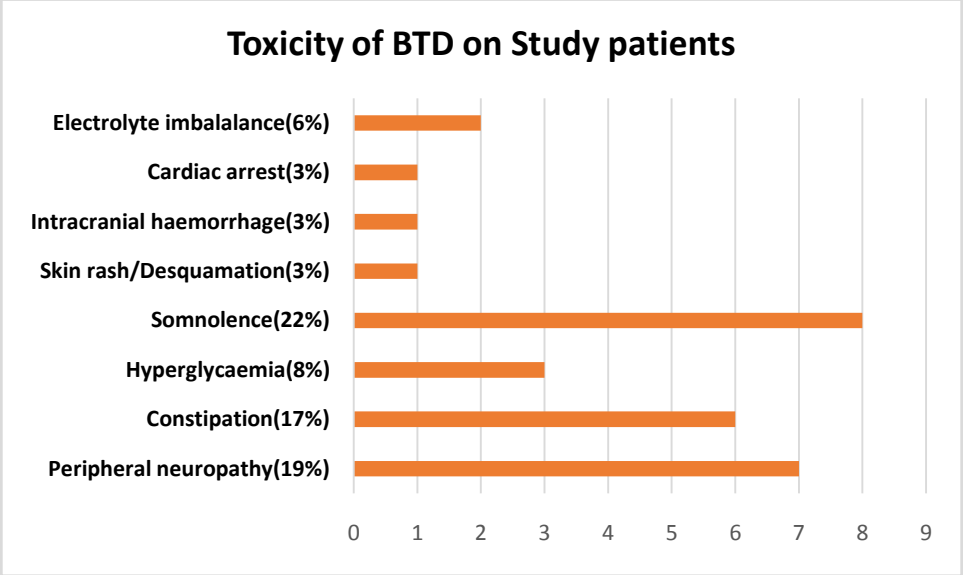

Figure 5. Bar Chart Showing Toxicity of Drug therapy on Study Patients

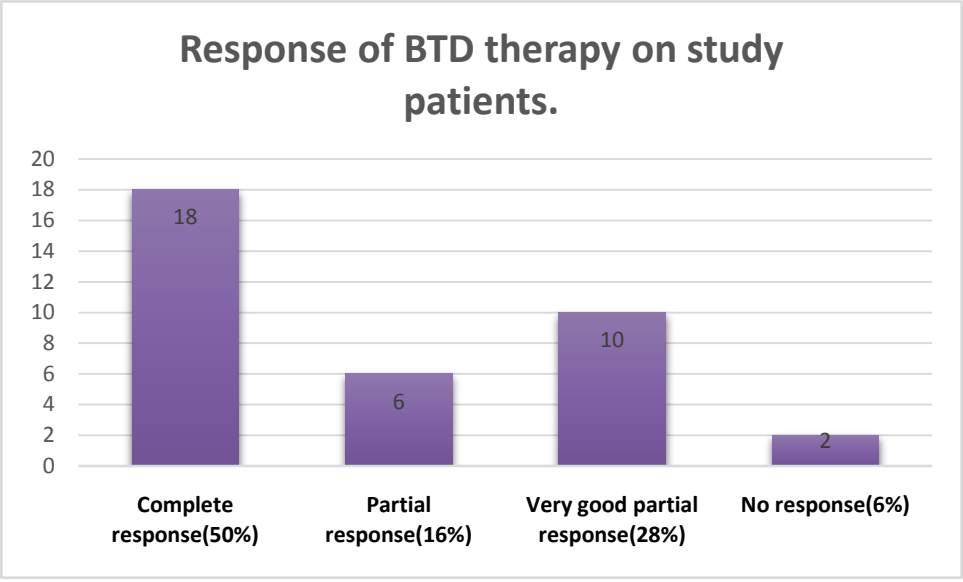

Figure 6. Bar Chart Showing IMWG Response Rate After 4 Cycles Of BTD Chemotherapy.

4. Discussion

The mean age was 58.04 (SD±6.45) and median was 56 .Age ranged from 42-75 years. These findings are a little bit lower than study done by Rajkumar, blood, Vosle et al (2005), Lokhorst, Wolf and Sonneveld et al (2008), Dingli, Rajkumar, Nowakowski (2005). They found the median (range) age 65 (38-83), 59 (34-65) and 66 (36-78).[8] In the present study , number of male was 25 (70%) and female was 11 (30%) and male to female ratio was 2.3:1. Sex ratio of the patient vary widely, the male –female ratio in studies by Rajkumar, blood, Vosle et al (2005), Lokhorst, Wolf and Sonneveld et al (2008), Dingli, Rajkumar, Nowakowski(2005) are 1:1,2:1 and 1:1 respectively. [13,15,17] Most of the patients(33%) were business men by profession; other frequent occupation was service holder(28%), House wife (20%) and doctor(3%), farmer & teacher were 8% each.

All of the patients (36) presented with weakness, followed by 89% patients had bone pain and 28% noticed weight loss. On examination, 97% of patients had anaemia, 42% had evidence of infection and renal impairment was found in 16 (44%) cases. Only 4(11%) patients suffered from neuropathy. Where Khan MA, Sarker S, Kabir A, Hasan M, Haque M D (2002) found 100% of patient had bone pain, 77% had anaemia, 41% had infection and 18% had renal impairment. [11,16,17,18,21-24]

In this study population (36), mean ESR before chemotherapy was 94.7mm in Ist hour, where after treatment at 6 weeks and 12 weeks were 32 and 17.30 mm in Ist hour respectively. Before treatment mean Hb concentration was only 8.5g/dl which was increase to 10.57 g/dl and 11.84g/dl at 6 and 12 weeks. Where Khan MA, Sarker S, Kabir A, Hasan M, Haque M D (2002) showed 86.4% had high ESR (>85 mm in 1st hour) and 82% of patient had Hb<10gm/dl. [6,21-24]

Among the study population, mean S. calcium before chemotherapy was 9.65mg/dl which gradually went down to 9.32mg/dl and 9.10mg/dl at 6 weeks & 12 weeks respectively. At diagnosis, mean of S. creatinine, S. albumin, S.calcium and β2 microglobulin were 2.5 mg/dl, 28.12 gm/L, 9.65 mg/dl and 4.55mg/L respectively. But at 12 weeks mean were 1.45 mg/dl, 34.36 gm/L, 9.10mg/dl & 2.6mg/L respectively. In our study only 2 patients (6%) had hypercalcaemia, where Khan MA, Sarker S, Kabir A, Hasan M, Haque M D (2002) found 18%. [6,7,8,13,23,24,25]

During treatment 8 patients (22%) suffered from somnolence, 7(19%) had Peripheral neuropathy (17%) and 6 patients complained of constipation. We found 8% of suffered from hyperglyecaemia,, electrolyte imbalance (6%), life threatening intracranial haemorrhage, cardiac arrest and rash occurred in one patient (3%) respectively. Sundar Jagannath, Brian G. M. Durie, Jeffrey Wolf, Elber Camacho, David Irwin, Jose Lutzky, Marti McKinley et al. found the most common adverse events sensory neuropathy (31%), constipation (28%), myalgia (28%) and fatigue (25%). [3,7,13,23,25]

Out of 36 patients, complete response achieved in 18 patients (50%), where 6(16%),10(28%) and 2(6%) patients belonged to partial, very good partial and no response respectively. The overall response rate was 94%. Sundar Jagannath, Brian G. M. Durie, Jeffrey Wolf, Elber Camacho, David Irwin, Jose Lutzky, Marti McKinley et al. study showed response rate (CR + PR) was 88%, with undetectable paraprotein (CR) in 6% and All 32 patients completed the first two cycles of Bortezomib alone, of whom 3% achieved CR, 9% VGPR, and 28% PR. [11] Two patients (6%) died during treatment, 1 patient due to intracranial haemorrhage and another from cardiac arrest.

5. Conclusion

Bortezomib, Thalidomide, Dexamethasone (BTD) is well-tolerated and highly effective regimen for frontline treatment of MM. Its safe with acceptable adverse events profile. This combination has markedly improve overall response (OR), long progression free survival (PFS) and overall survival (OS) across in all risk groups. Since the depth of response to treatment correlates with outcomes. Future longitudinal studies involving larger number of patients with cytogenetic assays and histopathological correlation in high risk Myeloma patients will help in better understanding of the treatment outcome in MM. [25]

Ethical Approval

The study was approved by the Institutional Ethical Committee of Bangabandhu Sheikh Mujib Medical University (BSMMU).

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Conflict of Interest

Authors have no conflict of interest.

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