

Evidence-based supportive care in multiple myeloma

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ABSTRACT

Multiple myeloma (MM) is a hematological malignancy characterized by an abnormal clone of plasma cells in the bone marrow. MM and its therapy increase the risk of complications like anemia, osteolytic lesions, pain, infections, and renal abnormalities in MM patients. Supportive care for MM patients improves the quality of life. Treatment with bisphosphonates decreases skeletal-related events. Vertebroplasty and kyphoplasty are done in cases of vertebral compression fractures. Prophylactic antibiotics and antivirals can decrease infections related to morbidity. Plasmapheresis in patients with renal dysfunctions decreases dialysis dependency and improve quality of life.

ARTICLE HISTORY

Received 31 December 2019
Accepted 15 May 2020

KEYWORDS

Multiple myeloma; supportive care; bisphosphonates; kyphoplasty; infections; plasmapheresis; peripheral neuropathy; quality of life

1. Introduction

Multiple myeloma (MM) is the second most common hematological malignancy in the USA. In 2016, approximately 30,330 new cases of MM were diagnosed and less than 47% of these patients are expected to live beyond 5 years [1]. The elderly make up a large number of the cases with the median age at the time of diagnosis is 70 years. The standard treatment for MM is to improve quality of life, prolong progression-free survival (PFS), and overall survival (OS). Autologous stem cell transplant (ASCT) improves stem cell response rate and duration of response after drug induction therapy, while consolidation and maintenance therapies after ASCT further improve patient quality of life and prolong PFS. For transplant-ineligible patients, low toxicity regimens are used to improve their quality of life. In spite of the advent of novel agents, MM is associated with a significant decline in quality of life due to the treatment and its side effects. Some of the common complications of MM include anemia, lytic bone lesions, infections, hypercalcemia, and renal failure.

Health-related quality-of-life (HRQoL) is severely affected in elderly patients by complications like lytic bone lesions, infections, peripheral neuropathy, and renal failure, when measured by the fatigue scale Functional Assessment of Cancer Therapy-Fatigue (FACT). Treatment of these complications improves patients' physical, psychological, and social well-being [2]. Lytic bone lesions in MM patients increase the risk of skeletal-related events (SRE) like fractures, pain, and

spinal cord compression leading to poor quality of life. Bisphosphonates, radiotherapy, and vertebral augmentation decrease pain intensity and improve HRQoL [3]. Renal insufficiency due to deposition of monoclonal-free light chains in the kidneys and hypercalcemia increases the chance of renal failure in patients with MM [4]. In our review, we combined clinical data focusing on supportive care management of complications that negatively impact HRQoL.

We performed a comprehensive literature search on articles published after 2000 using the following databases: PubMed/Medline, EMBASE/Elsevier, ClinicalTrials.gov, Wiley Cochrane library, and Web of Science. The literature search identified 400 articles focusing on supportive care for anemia, bone pain, infections, renal insufficiency, and peripheral neuropathy in MM patients. After a detailed screening, we finalized 36 articles to include in our manuscript.

2. Management of skeletal-related events in multiple myeloma patients

Sixty percent of MM patients develop pathological fractures, 40% patients develop them during the first year after diagnosis, and 20% have pathological fractures at presentation. The most commonly involved areas are vertebrae (49%), skull (35%), pelvis (34%), and ribs (33%) [5]. Bisphosphonates are the standard treatment for bone disease in multiple myeloma. It reduces pain, pathological vertebral fractures, and SREs. Pamidronate 90 mg over 2–4-h infusion or

zoledronic acid 4 mg (over 15 min infusion) every 3 to 4 weeks is recommended [6]. Rosen et al. (2003) studied zoledronic acid (4 mg) in comparison with pamidronate (90 mg) in MM and breast cancer patients. The risk of any SRE was comparable in both groups in the MM patients (risk ratio, 0.932; $P = 0.593$) [7]. In network meta-analysis of 24 RCTs ($n = 7293$) there is no evidence of superiority of any single bisphosphonate although zoledronate was found to be better than placebo (HR 0.67, 95% CI 0.46 to 0.91) and etidronate (HR 0.56, 95% CI 0.29 to 0.87) for improving OS and vertebral fractures [8]. Bisphosphonates should be given with care in patients with renal insufficiency (Creatinine Clearance rate of 30 to 60 mL/min). Gareth et al. (2010, $n = 1960$) studied zoledronic acid and clodronic acid in MM patients. Zoledronic acid reduced mortality (hazard ratio [HR] 0.84, 95% CI 0.74–0.96; $p = 0.0118$), improved median overall survival (mOS) by 5.5 months and median progression-free survival (PFS) by 2 months when compared to clodronic acid [9].

Denosumab, a monoclonal antibody, inhibits receptor activator of nuclear factor kappa-B ligand (RANKL) and should be preferred in patients with renal insufficiency. Denosumab has been shown to be non-inferior to zoledronic acid in time to first SRE in a phase 3 trial of 1718 MM patients (HR 0.98, 95% CI 0.85–1.14; p of non-inferiority = 0.010) [10]. Although hypocalcemia occurs more frequently with denosumab as compared to zoledronic acid (17% vs. 12%), renal adverse events are less in denosumab vs. zoledronic acid (10% vs. 17%). Denosumab is also indicated for the treatment of hypercalcemia resistant to bisphosphonate.

Surgery is only indicated for high-risk fracture of long bones, spinal cord compression fractures, and unstable spine.

Radiotherapy is the treatment of choice in solitary plasmacytoma. In Valerie et al. (2011) retrospective study ($n = 84$ patients with solitary plasmacytoma) [11]. The median radiation dose was 45 gray (Gy) (range, 36–53.4 Gy), 92% of the patients responded with local control. Low dose radiotherapy (8 Gy x 1 fx or 10–30 Gy x 2–3 fx) can be used for uncontrolled bone pain, impending cord compression, and pathological fractures [12].

Vertebroplasty and balloon kyphoplasty are effective in reducing the pain of vertebral compression fractures. In a meta-analysis of 23 studies ($n = 923$ patients), vertebroplasty, kyphoplasty, or both showed that pain on a 10-point scale was decreased by 4.8 points after 1 week, 4.6 points after 1 year and 4.4 points beyond the first year [13].

3. Management of infections in multiple myeloma

MM patients have higher infection risks relative to the general population. Bloodstream infections in

hematological malignancies increase the risk of early mortality. Ramsus et al. (2018) study ($n = 1154$ MM patients) found that positive bloodstream culture was more common in first 6 months after MM diagnosis. Mostly organisms were bacterial (97%; 52% gram-positive and 48% gram-negative organisms) and fungal (3%) [14]. In Auguston et al. (2005) trial on ($n = 3,107$), MM patients found 10% early deaths were within 60 days of trial entry and 45% were related to infections [15]. Blimark et al. (2015) study ($n = 9253$ MM patients and $n = 34,931$ controls) showed 7-fold (HR = 7.1; 95% CI: 6.8–7.4) higher risk of developing bacterial infection and 10-fold (HR = 10.0; 95% CI: 8.9–11.4) higher risk of viral infections in MM patients as compared to controls, HR was 14.8 and 6.1, respectively [16].

Antibiotics: Pneumocystis jiroveci pneumonia (PCP) was seen in 25–45 cases/100,000 patient-year (Fillatre et al. 2014, $n = 293$) [17]. Kadee et al. (2013, $n = 1191$) reported the incidence of PCP as 0.42% (95% CI: 0.13–0.97) in patients receiving ASCT [18]. Stern et al. (2014, $n = 1000$) reported 85% reduced incidence of PCP in patients receiving prophylactic trimethoprim/sulfamethoxazole (TMP/SMX) after ASCT (RR of 0.15; 95% CI 0.04–0.62) [19].

Randomized clinical trial on MM patients ($n = 212$) receiving initial chemotherapy regimen (first 3 months) along with ciprofloxacin/ofloxacin (500 mg BD, $n = 64$), TMP/SMX (160 mg TMP and 800 mg SMX BD, $n = 74$) or observation (no antibiotics, $n = 63$) for 2 months, 12.5% (95% CI: 5.6–23.2), 6.8% (95% CI: 2.2–15.1), and 15.9% developed bacterial infection (95% CI: 7.9–27.3), respectively [20]. According to the European Society of Medical Oncology (ESMO) and European Myeloma network (EMN) guidelines, all patients should receive antibiotic prophylaxis for the first 3 months of therapy especially in patients receiving lenalidomide and pomalidomide. Stratification for Myeloma and Risk-Adapted Therapy (mSMART) and International Myeloma Working Group (IMWG) guidelines also recommend TMP/SMX prophylaxis during induction therapy for MM.

Antiviral: Multiple myeloma patients have increased risk of varicella-zoster virus (VZV) reactivation. Antiviral prophylaxis (acyclovir or valacyclovir) against herpes reactivation is recommended in patients on proteasome inhibitor (PI)-based therapy. In Leng et al. (2018) cohort study ($n = 70,687$), 52% patients receiving proteasome inhibitor (bortezomib &/or carfilzomib for ≥ 3 months) and herpes zoster prophylaxis with 84% adherence had fewer zoster infections (2.4%) in comparison to patients without herpes zoster prophylaxis (5.8%) (ARR 0.42; 95% CI: 0.31–0.56) [21]. Richardson et al. (2005) conducted a phase 3 APEX trial on 669 MM patients; Bortezomib ($n = 333$) vs dexamethasone ($n = 336$), the risk of herpes zoster infection was higher in patients receiving bortezomib

13% as compared to 5% with dexamethasone ($P < 0.001$) [22]. Dimopoulos et al. (2016, $n = 569$) reported increased incidence of pneumonia in Daratumumab group ($n = 286$) vs control group ($n = 283$), 7.8% vs. 8.2%, respectively [23]. Drgona et al. (2018) also reported an increased risk of VZV infection, in patients receiving daratumumab in combination with PI and/or corticosteroids. He suggested influenza vaccination in patients taking daratumumab and also prophylactic (val) acyclovir should be started 1 week before giving daratumumab and continued for 12 weeks after its discontinuation in VZV seropositive patients [24].

4. Management of renal insufficiency with plasmapheresis and hemodialysis

Renal dysfunction is present in 20–40% of MM patients among which 2–4% require renal dialysis [25]. Renal involvement occurs as a result of excessive serum-free light chains (sFLC) secretion that leads to cast nephropathy, hypercalcemia, acute tubular necrosis, or acquired Fanconi syndrome. An open, randomized clinical trial on 104 MM patients (baseline serum creatinine >2.3 mg/dL) treated with plasma exchange & chemotherapy, showed no improvement in GFR, dialysis dependence, or death. Recovery from dialysis occurred in 66% with plasma exchange as compared to 50% in the control group [26]. A meta-analysis of three randomized studies with patients on chemotherapy only ($n = 63$) or plasmapheresis and chemotherapy ($n = 84$) showed significantly lower 6-month dialysis dependency ratio; 15.6% with plasmapheresis and chemotherapy as compared to 37.2% in chemotherapy alone. No difference in OS was seen [27]. Alkhatib et al. (2017, $n = 147$) meta-analysis also

showed decrease dialysis dependency ratio in plasmapheresis group vs. control group (RR = 0.45; 95% CI, 0.23–0.86, $P = 0.02$) [28]. Hutchison et al. (2008, $n = 19$) reported that 14/19 patients who had extended HCO-HD and chemotherapy became hemodialysis independent at a median of 27 days (range 13–120 days) and had 50% reduction in sFLC while 11/14 patients had 75% reduction in sFLC [29]. Hutchison et al. (2012) revised study on 67 myeloma patients with dialysis-dependent renal insufficiency (RI) showed that the use of HCO-HD in combination with anti-myeloma therapy produced a sustained reduction of FLC in 67% of patients, and 63% patients became dialysis independent [30]. Current data supports the use of HCO-HD in combination with anti-myeloma therapy.

5. Management of peripheral neuropathy

Neuropathic pain is caused by anti-myeloma therapy (Bortezomib, Thalidomide), radiculopathy from direct compression, invasion of nerve by M-proteins, and amyloid deposition. Caravita et al. (2007) evaluated the incidence and severity of peripheral neuropathy (PN) in 179 MM patients (median age was 66.7 years) receiving bortezomib-based regimens. Grade ≥ 2 PN was seen in 73 patients (41%) and grade 3–4 in 32 (18%) patients [31]. In a phase II study by Richardson et al. (2003, $n = 202$ RRMM) bortezomib 1.3 mg/m² was given for 24 weeks. PN was seen in 63 (31%) patients with grade 3 PN in 25 (12%) patients [32]. Richardson et al. (2009) phase III APEX trial on 331 RRMM patients (median age 62 years). Treatment-emergent PN was seen in 124 patients (37%). Patients who had grade ≥ 2 PN ($n = 72$) undergo dose modification. Out of 41 patients

Table 1. Peripheral neuropathy and dose modifications of bortezomib and thalidomide.

Neuropathy grade	1		2		3	4
Peripheral sensory neuropathy ^a	Asymptomatic; loss of deep tendon reflexes or paresthesia		Moderate symptoms; limiting instrumental ADL		Severe symptoms; limiting self-care ADL	ADL Life-threatening consequences; urgent intervention indicated
Symptoms	Paresthesia, weakness, &/or loss of reflexes without pain or loss of function	Pain	Interfering with function, but not with activities of daily living	Pain	interfering with activities of daily living	sensory neuropathy that is disabling or leads to paralysis
Dose modification for bortezomib induced neuropathy	No action	25–50% reduction; 1.3 mg/m ² reduced to 1.0 or 0.7 mg/m ²	25–50% reduction; 1.3 mg/m ² reduced to 1.0 or 0.7 mg/m ²	Interrupt dose until resolution to grade 1; restart at 50% dose reduction	Interrupt dose until resolution to grade 1; restart at 50% dose reduction	Discontinue bortezomib
Dose modification for thalidomide induced neuropathy	Not Reported		50% dose reduction: 100 mg reduced to 50 mg		3–4 Treatment discontinuation until resolution to grade 1; restart at 50% dose reduction	Thalidomide discontinuation

^aNational Cancer Information Center Common Toxicity Criteria (NCIC-CTC), ADL = activities of daily living.

Table 2. Recommendations for peripheral neuropathy in multiple myeloma.

Drugs	Starting dose	Maximum dose	NCCN guidelines	NeuPSIG guidelines	CPS guidelines	GRADE recommendations
Tricyclic anti-depressants						
Nortriptyline; Desipramine	10–25 mg	50–150 mg	First line	First line	First line	First line
Selective serotonin reuptake inhibitors						
Duloxetine	20–30 mg	60–120 mg	First line	First line	Second line	First line
Venlafaxine	37.5 mg	75–225 mg	First line	First line	Second line	First line
Anticonvulsants						
Gabapentin	100–300 mg	900–3600 mg	First line	First line	First line	First line
Pregabalin	25 mg	600 mg	First line	First line	First line	First line
Topical agents (patches)						
Topical lidocaine 5% (daily)	3	3	NR	First line for LPNP	Second line for LPNP	Second line
Capsaicin 8% (3 months)	1–4	1–4	NR	NR	NR	Second line
Opioids agonists						
Morphine	10–15 mg every 4 hr	No max. dose	NR	Second line	Third line	Third line
Tramadol	50 mg (1or 2X/D)	100 mg (4X/D)	NR	Second line	Third line	Second line

CPS = Canadian Pain Society, GRADE = Grading of Recommendations Assessment, Development and Evaluation, LPNP = lLocalized peripheral neuropathy, NCCN = National Comprehensive Cancer Network, NeuPSIG = Neuropathic Pain Special Interest Group, NR = not reported.

who did not discontinue bortezomib, 29 patients (71%) had resolved PN in 78 days. Patients who discontinued bortezomib (n = 31), 65% patients (n = 20) had improved (n = 8) or resolved (n = 12) neuropathy in a median of 122 days [33]. Mileshekin et al. (2006) found that thalidomide causes neuropathy in MM patients and limits the treatment duration. In this study, 75 RRMM patients were involved and received thalidomide at a median dose of 373 mg/day. Thirty-one patients (41%) develop neuropathy within 24 weeks (range 2–60 weeks). Incidence rate was increased from 38% ± 14% at 6 months to 73% ± 16% at 12 months [34]. Dose modification guidelines for Bortezomib and thalidomide are given in Table 1. Drugs used for PN and their lines of recommendations according to different guidelines given in Table 2.

6. Conclusion

Multiple myeloma complications include anemia and end-organ damage that severely impacts health-related quality of life. Patients require symptomatic treatment of these complications to prolong their remission and decreasing morbidity while reducing mortality with anti-myeloma therapy.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the National Institutes of Health [Grant number – P30 CA023074].

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