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Presentation and Outcome of Patients with Multiple Myeloma (MM), Single Centre Experience from Windsor Essex Regional Cancer Centre

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Introduction: Outcomes for patients with multiple myeloma has significantly improved through the years. This is mainly related to the use of novel agents.

Methods: This is a retrospective study that reviewed presentation and outcome of 139 patients with multiple myeloma at the Windsor Essex Regional Cancer Centre from Jan. 1, 2015 to Dec. 31, 2019. Median age was 71 years and most patients had higher risk disease (65.5% either R ISS stage II or III). 30% had high risk FISH for myeloma including del.17p, t (4:14), t (14:16) and Gain (1q21). In terms of presentation, 38.8% had anemia (hemoglobin <100g/L), 18.7% had hypercalcemia, 74.1% had skeletal lytic lesions, 38.8% had pathologic fracture and 17.3% had plasmacytoma.

Results: Almost all (92%) of the patients were treated using at least one novel agent (proteasome inhibitor or immunomodulators [ImiDs]). Cyclophosphamide, bortezomib, and dexamethasone (CyBORd) was the most used treatment regimen (48.9%) followed by bortezomib, melphalan and prednisone (BMP) at 28.8% and lenalidomide, dexamethasone (LenDex) at 14.4%. With respect to response to therapy, 51.8% had at least Very good partial response (VGPR), while 9.4% had progressive disease. 33% had autologous stem cell transplant. After a median follow up of 2.4 years, median overall survival was 3.7 years. 2 years overall survival and relapse-free survival were 70% and 83%, respectively.

Discussion: Our study showed comparable outcome for patients with multiple myeloma despite older age and higher risk disease. Outcome is expected to improve with the introduction of more novel agents.

Keywords: multiple myeloma, proteasome inhibitors, immunomodulators

Introduction

Multiple myeloma was responsible for 1600 deaths in Canada in 2020 with an annual incidence of 3400 cases (<https://www.cancer.ca/statistics>). Although there are significant advances in its treatment, multiple myeloma is still an incurable disease. The discovery of novel therapeutic agents including proteasome inhibitors and immunomodulators made a huge improvement in the outcome of patients with multiple myeloma.¹

The newly utilized combination of monoclonal antibodies and dual novel agents has resulted in a dramatic improvement in response rate, minimal residual disease (MRD) negativity and survival.^{2,3} However, access to newer anti-myeloma drugs is variable among different countries as well as provinces. This is likely in part responsible for the differences in patient outcomes among different institutions.

In this retrospective chart review, data on demographics, presentation and outcome of patients with multiple myeloma treated at the Windsor Essex Regional Cancer Centre are described. Outcome metrics including median overall survival and relapse-free survival were compared with the outcomes from local as well as international institutions.

Methods

The study is a retrospective chart review on 139 patients diagnosed and treated for multiple myeloma from Jan. 1, 2015 to Dec. 31, 2019 at the Windsor Essex Regional Cancer Centre. Information on demographics, presentation, treatment and outcome was collected.

The Revised International Staging system (R ISS) was included whenever information was available using the IMWG definition. Patients with high-risk FISH were defined as having one of the following: del.17p, t (4; 14), t (14; 16) and Gain (1q21). Response rates were classified as complete remission (CR), Very good partial response (VGPR), stable disease and progressive disease based on the IMWG criteria.^{4,5}

Continuous variables are presented as median (interquartile range [IQR]) and categorical variables are reported as frequency (percentage). Time to all-cause mortality and relapse were assessed graphically using Kaplan-Meier curves. Median survival time was determined using the time where the Kaplan-Meier survival curve crossed the 50% threshold. Characteristics associated with death and relapse were assessed using hazard ratios obtained from univariable Cox proportional hazards models. Two-sided p-values <0.05 were considered statistically significant. All analyses were run using R version 4.0.2.

Results

A total of 139 patients with multiple myeloma were treated at the Windsor Essex Regional Cancer Centre from Jan. 1, 2015 to Dec. 31, 2019.

Median age was 71 years, ranging from 63–78 years, with 52% male. Most patients had higher risk disease (65.5% either R ISS stage II or III). 30% had high risk FISH for myeloma including del.17P, t (4:14), t (14:16) and Gain (1q21). In terms of presentation, close to half (47%) had moderate to severe renal impairment (eGFR < 60mL/min/1.73m²), 38.8% had anemia (hemoglobin <100g/L), 18.7% had hypercalcemia, 74.1% had skeletal lytic lesions, 38.8% had pathologic fracture and 17.3% had concurrent plasmacytoma (Table 1).

Table 1 Baseline Characteristics of Patients with Multiple Myeloma

	Overall (N=139)
Age (Years)	
Median (IQR)	71 (63, 78)
Sex	
Male	72 (51.8%)
Female	67 (48.2%)
Revised International Staging System (R-ISS)	
I	8 (5.8%)
II	66 (47.5%)
III	25 (18.0%)
N/A	40 (28.8%)
Glomerular filtration rate (mL/min/1.73m²)	
>90	26 (18.7%)
60–90	46 (33.1%)

(Continued)

Table I (Continued).

	Overall (N=139)
30–59	38 (27.3%)
15–29	14 (10.1%)
<15	13 (9.4%)
Missing	2 (1.4%)
Ionized calcium (mmol/L)	
Normal (≤ 1.29)	107 (77.0%)
Elevated (> 1.29)	26 (18.7%)
Missing	6 (4.3%)
Hemoglobin (g/L)	
≥ 100	85 (61.2%)
< 100	54 (38.8%)
Lactate dehydrogenase (LDH) (U/L)	
Normal (< 234)	110 (79.1%)
Elevated (≥ 234)	25 (18.0%)
Missing	4 (2.9%)
Skeletal lytic lesions	
Yes	103 (74.1%)
No	35 (25.2%)
Missing	1 (0.7%)
Pathologic fracture	
Yes	54 (38.8%)
No	84 (60.4%)
Missing	1 (0.7%)
Plasmacytoma	
Yes	24 (17.3%)
No	114 (82.0%)
Missing	1 (0.7%)
Myeloma Fluorescence In Situ Hybridization	
Negative	45 (32.4%)
High Risk	43 (30.9%)
Standard Risk	3 (2.2%)
N/A	48 (34.5%)

Almost all (92%) of the patients were treated using at least one novel agent (proteasome inhibitor or ImiDs). Cyclophosphamide, bortezomib, and dexamethasone (CyBorD) was the most commonly used treatment regimen (48.9%) followed by bortezomib, melphalan and prednisone (BMP) at 28.8% and lenalidomide, dexamethasone (LenDex) at 14.4%. Only five patients received melphalan-dexamethasone. 33% had autologous stem cell transplant and 31% were on maintenance therapy for a median of 10 months (Table 2).

With respect to response to therapy, 51.8% had at least Very good partial response (VGPR) of which 12.2% had Complete response (CR). 9.4% had progressive disease. The rest include partial response, stable disease and missing (Table 2).

Table 2 Treatment and Outcome of Patients with Multiple Myeloma

	Overall (N=139)
Initial chemotherapy regimen	
Lenalidomide-Dexamethasone	20 (14.4%)
Bortezomib-Melphalan-Prednisone	40 (28.8%)
Cyclophosphamide-Bortezomib-Dexamethasone	68 (48.9%)
Melphalan-Dexamethasone	5 (3.6%)
Missing	6 (4.3%)
Number of chemotherapy cycles	
Median (IQR)	5 (4, 7)
Missing	1 (0.7%)
Best Response	
Complete response	17 (12.2%)
Very good partial response	55 (39.8%)
Partial response	31 (22.3%)
Stable disease	12 (8.6%)
Progressive disease	13 (9.4%)
Missing	11 (7.9%)
Toxicity requiring dose reduction/stop	
Yes	28 (20.1%)
No	94 (67.6%)
N/A	10 (7.2%)
Missing	7 (5.0%)
Toxicity type	
Peripheral neuropathy	3 (2.2%)
Diarrhea	3 (2.2%)
Fatigue	1 (0.7%)

(Continued)

Table 2 (Continued).

	Overall (N=139)
Cytopenia	4 (2.9%)
Other	15 (10.8%)
Multiple types	3 (2.2%)
N/A	94 (67.6%)
Missing	16 (11.5%)
Palliative radiation	
Yes	64 (46.0%)
No	73 (52.5%)
Missing	2 (1.4%)
First autologous stem cell transplant	
Yes	46 (33.1%)
No	90 (64.7%)
Missing	3 (2.2%)
Tandem stem cell transplant	
Yes	3 (2.2%)
No	134 (96.4%)
Missing	2 (1.4%)
Maintenance therapy	
Yes	44 (31.7%)
No	92 (66.2%)
Missing	3 (2.2%)
Maintenance chemotherapy regimen	
Lenalidomide	35 (25.2%)
Bortezomib	3 (2.2%)
Ixazomib	1 (0.7%)
Lenalidomide-Ixazomib	4 (2.9%)
Lenalidomide-Dexamethasone	1 (0.7%)
N/A	95 (68.3%)
Duration of maintenance therapy (months)	
Median (IQR)	10 (5, 20)
Missing	95 (68.3%)

(Continued)

Table 2 (Continued).

	Overall (N=139)
Palliative care referral	
Yes	41 (29.5%)
No	97 (69.8%)
Missing	1 (0.7%)

Patients were followed for a median of 2.4 years with 61 deaths and 31 relapse events. Median overall survival was 3.7 years. Two years overall survival and relapse-free survival were 70% and 83%, respectively. One year survival probability was 80% (Figures 1 and 2).

Cox regression showed hypercalcemia as the only variable significantly associated with increased risk of relapse (HR 2.76, 95% CI 1.28–5.97, P value 0.009). On the other hand, older age (HR 1.03 per year, 95% CI 1.05–1.05, P value 0.02), response inferior to VGPR (stable disease/partial response) (HR 2.87, 95% CI 1.57–5.27, P<0.0001) and progressive disease (HR 10.25, 95% CI 4.99–21.06, P<0.0001) were significantly associated with risk of death. In addition, having autologous stem cell transplant (HR 0.18, 95% CI 0.08–0.38, P value 0.0001) and being on maintenance therapy (HR 0.25, 95% CI 0.12–0.51, P < 0.0001) were significantly associated with reduced risk of dying (Tables 3 and 4).

Discussion

Despite its limitations including small sample size and retrospective design with missing variables, the study revealed important information on the presentation, treatment and outcome of patients with multiple myeloma at the Windsor

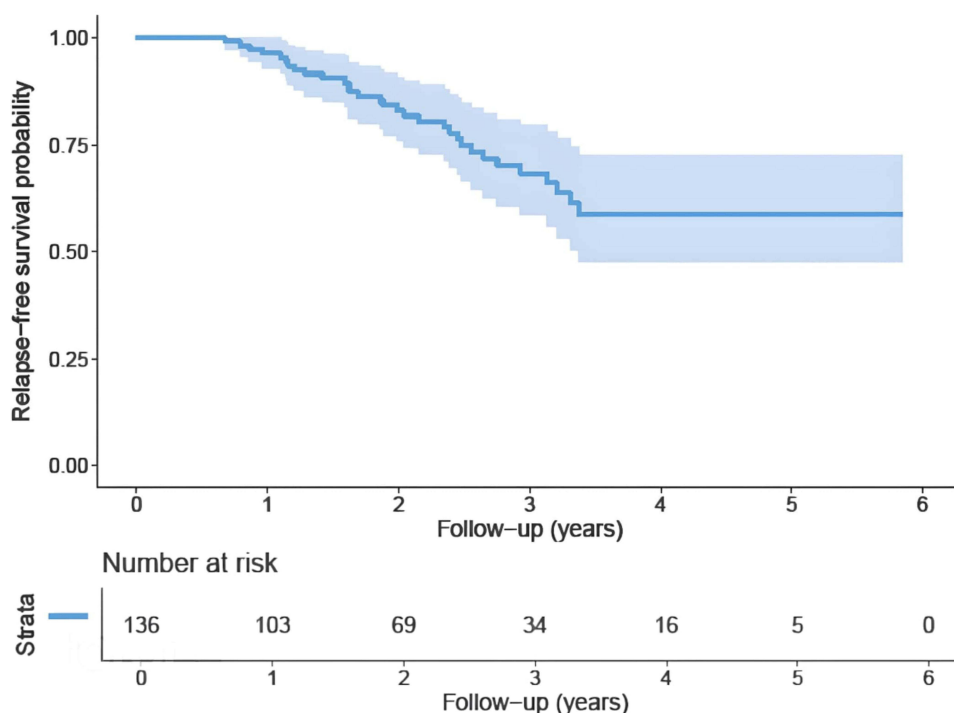


Figure 1 Shows The Kaplan-Meier curve for patients' relapse-free survival in years.

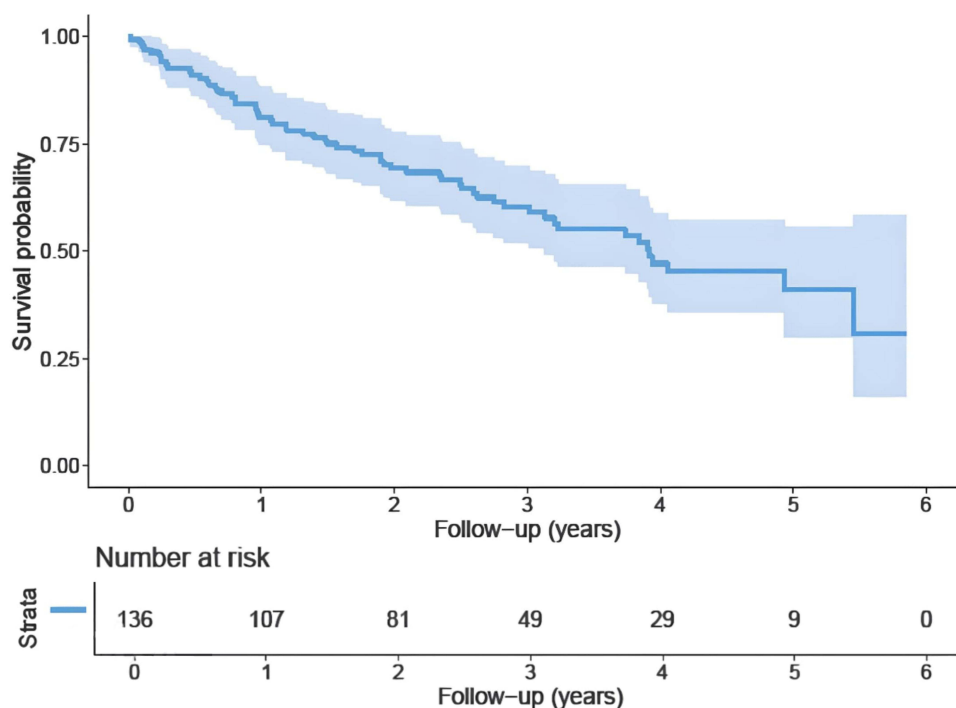


Figure 2 Shows The Kaplan-Meier curve for patients' overall survival in years.

Essex Regional Cancer Centre. Outcome of patients in this study is comparable with other centres in Canada as well as patients internationally treated with similar regimen. However, the outcome is inferior to those centres that used dual novel agents with or without monoclonal antibody.^{6,7}

A retrospective study from Alberta multiple myeloma registry on 147 patients with median age of 73 years showed median overall survival of 3.3 years for those on CyBorD regimen, which is comparable to our study (ASH poster 2020). Another study from the Swedish myeloma registry on 4904 patients from 2008 to 2015 showed median overall survival

Table 3 Hazard Ratios for Baseline Characteristics and the Outcome of Relapse

Variable	Value	Unadjusted			
		Hazard Ratio	95% CI		P-value
Age, per year		0.99	0.96	1.02	0.48
Sex					
	Female	0.73	0.36	1.49	0.39
	Male	1.00	(referent)		
R-ISS					
	I or II	1.00	(referent)		
	III	2.20	0.88	5.45	0.09
Ionized calcium					
	Normal (≤ 1.29)	1.00	(referent)		
	Elevated (> 1.29)	2.76	1.28	5.97	0.0099

(Continued)

Table 3 (Continued).

Variable	Value	Unadjusted			
		Hazard Ratio	95% CI		P-value
Glomerular filtration rate					
	≥60	1.00	(referent)		
	<60	1.62	0.78	3.33	0.19
Pathologic fracture					
	No	1.00	(referent)		
	Yes	1.50	0.74	3.06	0.26
Hemoglobin					
	<100	1.37	0.66	2.82	0.40
	≥100	1.00	(referent)		
Best response					
	Complete or very good partial response	1.00	(referent)		0.90
	Partial response or stable disease	0.94	0.42	2.13	
	Progressive disease	1.72	0.40	7.39	
Autologous stem cell transplant					
	No	1.00	(referent)		
	Yes	0.71	0.34	1.46	0.35
Maintenance therapy					
	No	1.00	(referent)		
	Yes	0.80	0.38	1.66	0.54

of 3.4 years for those patients older than 65 years of age which is again comparable with our outcome. However median overall survival was much higher at 7.7 years for those patients 65 years or younger suggesting the strong impact of age on survival.⁶ Another retrospective study on 1000 patients from the Emory myeloma database from January 2007 to August 2016 showed much higher median overall survival of 10.5 years. However, these patients were treated with a regimen that has dual novel agents [RVD: Revlimid (ImiD) and velcade (proteasome inhibitor)]. In the same study response of VGPR or better was also much higher at 89% compared with 51% in our study.⁷ This underscores the importance of using multiple novel agents to get a deeper response in the initial treatment of multiple myeloma. With the discovery of more and more novel therapies for the treatment of multiple myeloma, access to these drugs will be critical.

This is clearly demonstrated in the dramatic response seen with the combination of monoclonal antibody, daratumumab, and dual novel agents (ImiDs or proteasome inhibitors) in the frontline treatment of patients with multiple myeloma with a complete response rate of up to 79% and minimal residual disease (MRD) negativity of 14–24%.^{2,3}

The most widely used, currently funded, first-line treatment regimen for transplant eligible patients with multiple myeloma in Windsor Essex is CyBorD. Whereas BMP and recently LenDex are funded and commonly used as first-line therapy for those who are ineligible for autologous stem cell transplant. (Systemic Treatment - Quality Based Procedure, Cancer Care Ontario; <https://www.cancercareontario.ca/en/cancer-treatments/chemotherapy/funding-reimbursement/systemic-treatment-quality-based-procedure>).

Table 4 Hazard Ratios for Baseline Characteristics and the Outcome of All-Cause Mortality

Variable	Value	Unadjusted			
		Hazard Ratio	95% CI		P-value
Age, per year		1.03	1.01	1.05	0.02
Sex					
	Female	0.89	0.54	1.48	0.65
	Male	1.00	(referent)		
R-ISS					
	I or II	1.00	(referent)		
	III	0.98	0.43	2.27	0.97
Ionized calcium					
	Normal (≤ 1.29)	1.00	(referent)		
	Elevated (> 1.29)	1.53	0.85	2.78	0.16
Glomerular filtration rate					
	≥ 60	1.00	(referent)		
	< 60	1.41	0.84	2.37	0.19
Pathologic fracture					
	No	1.00	(referent)		
	Yes	0.71	0.42	1.22	0.22
Hemoglobin					
	< 100	1.33	0.80	2.22	0.27
	≥ 100	1.00	(referent)		
Best response					
	Complete or very good partial response	1.00	(referent)		< 0.0001
	Partial response or stable disease	2.87	1.57	5.27	
	Progressive disease	10.25	4.99	21.06	
Autologous stem cell transplant					
	No	1.00	(referent)		
	Yes	0.18	0.08	0.38	< 0.0001
Maintenance therapy					
	No	1.00	(referent)		
	Yes	0.25	0.12	0.51	< 0.0001
Relapse (time-varying covariate)					
	No	1.00	(referent)		
	Yes	2.03	0.96	4.29	0.06

Although access to combination of novel agents is slowly improving, the data are compelling to incorporate multiple novel agents and monoclonal antibodies in the front-line setting. This will result in deeper response and higher rate of MRD negativity which in turn will have positive impacts on survival.^{2,3} Regulatory agents will need to consider this emerging scientific evidence and cost-benefit implications for society in deciding drug access, particularly in multiple myeloma.

Hypercalcemia was the only variable significantly associated with higher risk of relapse (HR 2.76, 95% CI 1.28–5.97, P 0.009) but not death in our study. Other studies on patients with symptomatic MM showed inferior survival in those patients with hypercalcemia.⁸

In our study, older age and poor response to therapy, particularly progressive disease (HR 10.2, 95% CI 4.99–21, P < 0.0001) were significantly associated with higher risk of death. On the other hand, those with autologous stem cell transplant had significantly lower risk of dying (HR 0.18, 95% CI 0.08–0.38, P < 0.0001). This could be associated with selection bias as patients who had autologous stem cell transplant are generally younger and healthier. Better survival for those on maintenance therapy can also be subjected to similar bias as patients who live longer are more likely to be on maintenance. Nevertheless, survival benefit for autologous stem cell transplant as well as maintenance therapy was demonstrated in several other studies.^{4,9–11}

The impact of relapse on survival as a time-dependent variable was close to statistical significance but not quite, unlike other studies which showed early relapse as a risk for poor survival.¹²

Finally, despite the continuous effort of the scientific community in finding new and novel treatment options for multiple myeloma, studies still suggest that the outcome of patients with 17p deletion and t(4; 14) has not improved dramatically.^{13,14} This underscores the need for continued bench to bedside collaboration between scientists and clinicians for continued breakthrough in the fight against myeloma.

In conclusion, our study showed comparable outcomes for patients with multiple myeloma treated with similar treatment regimen in other centres. However, improved patient outcomes were observed with newer regimens that incorporate monoclonal antibodies and dual novel agents. As more and more novel drugs are introduced to the armament against the disease, it is expected that access to these drugs will affect outcomes. We recommend a prospective myeloma registry to acquire more comprehensive information as well as improved access to combination of novel agents and monoclonal antibodies to improve the outcome of our patients with multiple myeloma.

Ethical/Copyright

The study was cleared by the Windsor Regional Hospital (WRH) Ethics Review Board and supported by the Schulich-Windsor Opportunities for Research Excellence Program (SWORP). The study was exempt from informed consent as it was judged to not involve more than minimal risk as approved by the ethics review board of WRH. Maximum precaution was used to protect patient confidential data. The study was conducted in compliance with the Declaration of Helsinki.

Disclosure

The authors report no conflicts of interest in this work.

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