Critical Reviews in Oncology / Hematology 130 (2018) 27–35

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Early mortality in myeloma patients treated with first-generation novel agents thalidomide, lenalidomide, bortezomib at diagnosis: A pooled analysis

Sara Bringhen[a], Massimo Offidani[b], Salvatore Palmieri[c], Francesco Pisani[d], Rita Rizzi[e], Stefano Spada[a], Andrea Evangelista[f], Nicola Di Renzo[g], Pellegrino Musto[h], Magda Marcatti[i], Roberto Vallone[j], Sergio Storti[k], Annalisa Bernardini[a], Riccardo Centurioni[l], Enrico Aitini[m], Angelo Palmas[n], Ombretta Annibali[o], Emanuele Angelucci[p], Paola Ferrando[q], Anna Baraldi[r], Stefano Rocco[s], Alessandro Andriani[t], Agostina Siniscalchi[u], Valerio De Stefano[v], Vittorio Meneghini[w], Antonio Palumbo[a,1], Sara Grammatico[x], Mario Boccadoro[a], Alessandra Larocca[a,*]

[a] Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy
[b] Clinica di Ematologia, AOU Ospedali Riuniti di Ancona, Ancona, Italy
[c] Divisione di Ematologia con Unità TMO, AO Cardarelli, Napoli, Italy
[d] Hematology and Stem Cell Transplant Unit, Regina Elena National Cancer Institute, Rome, Italy
[e] Section of Hematology with Transplantation, Department of Emergency and Organ Transplantation, University of Bari Medical School, Bari, Italy
[f] Unit of Clinical Epidemiology, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino and CPO Piemonte, Torino, Italy
[g] U.O. Ematologia, P.O. V. Fazzi, Lecce, Italy
[h] Scientific Direction, IRCCS-CROB, Referral Cancer Center of Basilicata, Rionero in Vulture (PZ), Italy
[i] U.O. Ematologia e Trapianto di Midollo, IRCCS Ospedale San Raffaele, Milano, Italy
[j] Azienda Ospedaliera Gaetano Rummo, Immunoematologia e Trasfusione, Benevento, Italy
[k] UOC Oncoematologia Fondazione di Ricerca e Cura Giovanni Paolo II, Campobasso - Università Cattolica del Sacro Cuore, Campobasso, Italy
[l] U.O.C. Medicina Interna Civitanova Marche, Italy
[m] Struttura Complessa di Oncologia Medica ed Ematologia, Azienda Ospedaliera Carlo Poma, Mantova, Italy
[n] Divisione Ematologia, Ospedale San Francesco, Nuoro, Italy
[o] UOC Ematologia e Trapianto di Cellule Staminali, Università Campus Bio-Medico, Roma, Italy
[p] IRCCS Azienda Ospedaliera Universitaria San Martino - IST Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy
[q] S.C. Oncologia, Ospedale A. Manzoni, Lecco, Italy
[r] SOC Ematologia ospedale SS Antonio e Biagio e C. Arrigo Alessandria, Italy
[s] Divisione di Ematologia, AO Cardarelli, Napoli, Italy
[t] UOSD di Ematologia, ASL Roma1, Roma, Italy
[u] UOC Ematologia Ospedale S. Eugenio Roma, Italy
[v] Istituto di Ematologia, Università Cattolica, Fondazione Policlinico Universitario A. Gemelli, Roma, Italy
[w] Hematology Unit, Department of Medicine, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[x] Hematology, "Sapienza" University of Rome, Italy

ARTICLE INFO

Keywords:
Multiple myeloma
Toxic death
Early mortality
Newly diagnosed
Transplant-Ineligible
New drugs
Bortezomib
Lenalidomide

ABSTRACT

Introduction: Early toxic death (≤60 days of diagnosis) in elderly multiple myeloma (MM) patients is attributable to active disease, age and co-morbidities. Rate of early toxic deaths is 10% with conventional chemotherapy mainly due to infection and renal failure. Novel agents have improved MM outcome at the expense of newer toxicity.

Methods: We analyzed 1146 individual patient data to assess toxic deaths during induction treatment with first-generation novel agents thalidomide, lenalidomide, bortezomib.

Results: During first-line therapy, 119/1146 patients (10%) died for any cause, and 47/1146 (4%) due to toxicity, including 12/1146 (1%) early deaths. The 24-month cumulative incidence was 4.1% without any

* Corresponding author at: Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Via Genova 3, Torino, Italy.
E-mail address: alessandra.larocca@unito.it (A. Larocca).
[1] Currently a Takeda employee.

https://doi.org/10.1016/j.critrevonc.2018.07.003
Received 17 January 2018; Received in revised form 10 May 2018; Accepted 11 July 2018

Thalidomide

difference between bortezomib (18/503 patients, 4%) and lenalidomide (29/643patients, 5%; p = 0.31). Toxic deaths occurred in 34/1039 (3%) patients < 80 years and 13/107 (12%) patients ≥80 years. Causes were cardiac events (28%), infections (26%) and vascular complications (15%). In a multivariate analysis, older age and unfavorable ISS stage increased the risk of death.

Conclusion: First-generation novel agents significantly reduced toxic deaths compared to conventional chemotherapy. One third of deaths during first-line therapy were due to cumulative drug-related toxicities, thus supportive approaches and prevention strategies should be optimized. The higher mortality rate for toxicity in octogenarians confirms the need for a careful frailty assessment.

1. Introduction

In patients with multiple myeloma, significant improvements in survival have been obtained following the introduction of high-dose melphalan and autologous stem-cell transplantation, as well as with bortezomib and the immunomodulatory agents thalidomide and lenalidomide (Kumar et al., 2008; Palumbo and Anderson, 2011; Pulte et al., 2011). A population-based survival of European hematological malignancies before and after the introduction of novel agents showed that the improvement in survival was primarily restricted to patients younger than 65 years, while the benefit was less evident in older patients. Furthermore, little information is available regarding the impact of these new agents on early mortality.

Studies on causes of death among elderly patients are difficult to conduct due to low compliance. Studies conducted before the introduction of novel agents found a 2-month mortality of approximately 10%. In patients treated with novel agents, this rate decreased to approximately 6% (Morgan et al., 2011). The most common causes of death were renal failure and infections, mainly pneumonia and sepsis.

Many factors may contribute to increase the risk of death due to toxicity (toxic death) in myeloma. Age is one such factor. In the study by Augustson et al., 60% of patients who died within 2 months from start of treatment were older than 65 years. In the study by Dimopoulos et al., the incidence of early death was 14% in patients older than 80 years and 3% in those younger than that (Dimopoulos et al., 2012). In addition, older people are at high risk of developing frailty, that is a state of increased vulnerability, with cumulative deficits in several physiological systems, and a diminished resistance to stressors, such as myeloma and its treatment (Clegg et al., 2013). Age and geriatric assessment are the most sensitive predictors of frailty. The cut-off age of 80 years was found to identify frail myeloma patients that are at higher risk of death, disease progression, non-hematologic toxicities, and treatment discontinuation. However, irrespective of age, the presence of either a functional decline or the presence of co-morbidities, may identify frail patients. Approximately one third of elderly MM patients at diagnosis are frail (Palumbo et al., 2015, 2014b).

Active disease is a particularly important contributing factor to early mortality, because it may cause anemia, thrombocytopenia, neutropenia, skeletal disease with reduced mobility and impaired ventilation, hypercalcemia and renal impairment (Palumbo and Anderson, 2011). Therapy itself may further increase the risk of early death, by affecting renal and cardiac function and causing immunosuppression by damaging mucosal barriers and impairing both innate and specific cellular immunity. These adverse effects of therapy occur in the early stage of induction treatment, before achieving major reduction of tumor load and MM-related organ and tissue impairment. Consequently, induction treatment is associated with a high mortality risk (Augustson et al., 2005; Murakami et al., 2001).

In the era of novel agents, limited data are available on the risk, characteristics and predictability of early death in elderly patients. To address these issues, we analyzed individual patient data from 2 large multicenter randomized phase 3 trials. All patients received upfront first-generation novel agents, thalidomide, lenalidomide, bortezomib. The objectives were to: (1) evaluate the rate of death during first-line therapy, and particularly the risk of early death, (2) analyze the documented direct cause of death and (3) analyze the associated contributing factors.

2. Materials and methods

2.1. Patient population

A total of 1173 patients with newly diagnosed multiple myeloma not eligible for autologous transplantation for age or co-morbidities entered into Gruppo Italiano Malattie Ematologiche dell'Adulto and European Myeloma Network trials from May 2006 to September 2012, and were included in this analysis. Details on treatment regimens and results of these studies have been previously reported (Magarotto et al., 2016; Palumbo et al., 2014a). Briefly, in the GIMEMA MM-03-05 trial 511 patients were randomly assigned to receive 9 cycles of bortezomib, melphalan and prednisone (VMP) or bortezomib, melphalan, prednisone and thalidomide (VMPT) followed by continuous VT as maintenance. In the EMN01 trial 662 patients were randomized to lenalidomide and dexamethasone (Rd) or lenalidomide, melphalan and prednisone (MPR) or lenalidomide, cyclophosphamide and prednisone (CPR) followed by continuous R or RP as maintenance (Table 1). Trial protocols were approved by the ethics committee at each participating institution and the procedures were conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent before enrolment.

2.2. Assessment

Patient trial clinical report forms (CRFs) and adverse event (AE) –

Table 1
Characteristics of the trials includedin the analysis.

Trial	Patients (Total No.)	Age (Median, years)	Trial Dates	Induction treatment	Patients (No.)	Progression-free Survival (median, months)	Overall Survival
GIMEMA MM-03-05	511	71	2006–2009	VMPT-VT	254	35.3	61% at 5 years
				VMP	257	24.8	51% at 5 years
EMN-01	654	73	2009–2012	Rd	217	21	58% at 4 years
				MPR	217	24	65% at 4 years
				CPR	220	20	68% at 4 years

VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by continuous bortezomib-thalidomide as maintenance; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide-dexamethasone; MPR, lenalidomide-melphalan-prednisone; CPR, lenalidomide-cyclophosphamide-prednisone.