ELSEVIER

Critical Reviews in Oncology/Hematology 85 (2013) 162–192

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

The immunomodulatory agents lenalidomide and thalidomide for treatment of the myelodysplastic syndromes: A clinical practice guideline

Heather A. Leitch [a,*], Rena Buckstein [b], April Shamy [c], John M. Storring [d]

[a] *Hematology, St. Paul's Hospital and the University of British Columbia, Vancouver, Canada*
[b] *MDS Program, The Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada*
[c] *Hematology, Jewish General Hospital and McGill University, Montreal, Canada*
[d] *Hematology, Montreal General Hospital and the McGill University Health Centre, Montreal, Canada*

Accepted 10 July 2012

Contents

* Corresponding author at: 440-1144 Burrard Street, Vancouver, BC, Canada V6Z 2A5. Tel.: +1 604 684 5794; fax: +1 604 684 5704.
E-mail address: hleitch@providencehematology.com (H.A. Leitch).

1040-8428/$ – see front matter
http://dx.doi.org/10.1016/j.critrevonc.2012.07.003

Abstract

Background: Myelodysplastic syndromes (MDS) are clonal disorders that result in cytopenias and risk of acute myeloid leukemia. Incidence increases with age and more diagnoses are expected with the aging population. Treatment includes red blood cell transfusion for anemia. The immunomodulatory agents (imids) thalidomide and lenalidomide may induce transfusion independence. This guideline systematically reviews evidence on imids to treat MDS and makes evidence-based recommendations.
Methods: The literature and meeting abstracts were searched for phase 2–3 clinical trials. Data on efficacy, toxicity, and which patients benefit were extracted.
Results: 7019 citations on MDS management were identified. Thirteen publications and 9 meeting abstracts met eligibility criteria.
Conclusions: Lenalidomide is recommended as first line therapy in lower risk del5q MDS. There is insufficient evidence to recommend lenalidomide for treatment of higher risk del5q MDS or AML, or for any risk non-del5q MDS or AML. Combining lenalidomide with other agents is not recommended. Thalidomide is not recommended.

Keywords: Myelodysplastic syndrome (MDS); Systematic review; Clinical trials; Immunomodulatory agents; Lenalidomide; Thalidomide

1. Target population

The Canadian Consortium on Evidence-Based Care in MDS (CCMDS) is preparing a series of evidence-based guidelines addressing the treatment of adult patients with myelodysplastic syndromes (MDS) classified according to the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissue [1] and the French–American–British (FAB) classification of MDS [2]. These guidelines address patients with MDS of all subtypes, risk categories, comorbidities and performance status. The current guideline considers the use of the immunomodulatory agents (imids) thalidomide and lenalidomide in the treatment of MDS. Del5q MDS and MDS of either all or primarily non-del5q karyotype are addressed in separate sections of this guideline.

1.1. Questions

For both thalidomide and lenalidomide

1. In patients with MDS, what is the efficacy of thalidomide or lenalidomide alone or in combination with other agents as measured by response rate (transfusion independence (TI), improvement in transfusion requirements, improvement in hemoglobin level, platelet count or neutrophil count, complete remission [CR] and partial remission [PR]), response duration, time to progression (TTP), overall survival (OS), and quality of life (QOL)?
2. What toxicities/risks are associated with the use of thalidomide and lenalidomide?
3. Which patients are more likely to benefit from treatment with thalidomide or lenalidomide?

1.2. Introduction

The myelodysplastic syndromes are a heterogeneous group of clonal bone marrow malignancies characterized by ineffective hematopoiesis resulting in peripheral blood cytopenias and a variable risk of evolving to acute myeloid leukemia (AML). Features of lower risk MDS include an increase in programmed cell death of dysplastic hematopoietic cells, whereas higher risk MDS are characterized by an increased propensity toward clonal evolution in the malignant clone [3]. Resulting clinical manifestations include anemia requiring red blood cell (RBC) transfusion support in many patients. MDS is an acquired disorder primarily manifesting in older adults with a median age at diagnosis of 74. The only potentially curative therapy for MDS is allogeneic hematopoietic stem cell transplantation (SCT) but this procedure is generally limited to younger patients due to prohibitive toxicity. Treatments for the majority of MDS patients have until recent years been limited to supportive measures that aim to improve and optimize quality of life (QOL) and are generally not thought to impact on survival times [4].

The most widely used prognostic scheme in North America remains the International Prognostic Scoring System (IPSS), which risk-stratifies patients based on number of cytopenias, blast count in the marrow and karyotype analysis, allowing patients to be grouped into four categories: low, intermediate-1 (int-1), intermediate-2 (int-2) and high risk, with progressively decreasing predicted survival times and increasing risk of progression to AML [5]. For purposes of management, patients are often grouped into lower risk (low and int-1) in which non-leukemic deaths predominate, and higher risk (int-2 and high) in which leukemic deaths predominate. Prognostic systems for MDS are currently evolving and incorporate new information as it is shown to impact on patient outcome. The recognition of the importance of red blood cell (RBC) transfusion dependence as an adverse prognostic factor for AML evolution and overall survival [6] led to the development of the WHO-based Prognostic Scoring System (WPSS), which incorporates transfusion dependence into calculation of patient risk [7]. Both the IPSS and the WPSS use a limited number of cytogenetic abnormalities to denote karyotypic risk group. However, many additional cytogenetic abnormalities occur in MDS, and their impact on patient risk is addressed in a recently described Comprehensive Cytogenetic Scoring System [8]. The majority of the clinical studies done using imids to treat MDS predated these advances and