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Original Research

Infection risk with immunomodulatory and proteasome inhibitor–based therapies across treatment phases for multiple myeloma: A systematic review and meta-analysis

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Abstract ***Background:*** The objective of this review was to determine the impact of immunomodulatory drugs (IMiDs) and proteasome inhibitor (PI)–based therapy on infection risk in patients with myeloma across three treatment periods: induction, maintenance therapy and relapse/refractory disease (RRMM).

Methods: A systematic review and meta-analysis of randomised controlled trials (RCT) of IMiD and PI-based therapy versus conventional therapy from 1990 to 2015 using MEDLINE, EMBASE and CENTRAL was conducted. Study methods, characteristics, interventions, outcomes and rate of infection were extracted using a standardised tool.

Findings: Thirty RCTs of 13,105 patients fulfilled inclusion criteria. The rate of severe infection with the use of IMiD-based therapy was 13.4%, 22.4%, 10.5% and 16.6% for induction therapy for non-transplant- and transplant-eligible patients, maintenance therapy and therapy for RRMM, respectively. Rate of severe infection with PI-based induction in transplant-eligible patients was 19.7%. Compared to conventional therapy, use of IMiD-based induction therapy was associated with reduced risk for transplant patients (RR 0.76, $p < 0.01$). There was no significant difference with PI-based therapy. For maintenance therapy and RRMM, use of IMiD-based therapy was significantly associated with 74% and 51% increased risk of severe infection, respectively. Compared to thalidomide, bortezomib-based induction therapy and lenalidomide maintenance therapy were associated with increased risk of severe infection (RR 2.03, $p < 0.01$; RR 1.95, $p = 0.03$).

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Interpretation: The differential impact of myeloma therapies on risk for infection and the effect of treatment phases upon risk have now been established. Thalidomide is associated with the lowest risk of severe infection when used for induction and maintenance therapy.
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1. Introduction

Multiple myeloma is a plasma cell malignancy that is increasingly managed in aging populations [1]. Infection is a leading cause of morbidity and mortality in patients with myeloma with nearly 50% of early deaths due to infection [2]. Patients are at risk of infection due to patient, disease and treatment factors including cumulative effects of therapy and type of therapy contributing to additional risk [3]. The treatment for myeloma has undergone a paradigm shift over the last decade, with the routine use of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) as standards of care for induction therapy in combination with autologous haematopoietic stem cell transplant (ASCT) as consolidation for eligible patients.

Studies evaluating risk of infection with use of IMiD-based therapies in a mixed population of newly diagnosed and previously treated patients with myeloma have reported serious infection rates of up to 20% [4,5]. However, these studies do not account for clinical differences within their patient population nor determine infection risk compared with the use of conventional agents. In a recent longitudinal cohort study, combination conventional chemotherapy, high-dose melphalan, intravenous cyclophosphamide and cumulative doses of corticosteroids were independently associated with up to a threefold increased risk of infection, whilst the use of IMiD and PI were not associated with increased risk [6]. Patients with myeloma who undergo ASCT experience a higher incidence of fungal and viral infection compared to patients who do not receive ASCT [7,8]. The impact of the current generation of treatments on the risk for these infections remains unclear. Determination of baseline infection risk for IMiDs and PIs as the current standards of care is vital to facilitate future evaluation of infection risk for the next generation of myeloma therapies.

In a recent study of the patterns for infection in the era of immunomodulatory therapies, we identified that disease progression is a risk period for both bacterial and viral infections [6]. Studies evaluating risk factors, new approaches for prevention, and management of infection during this time period remain limited. Therefore, an assessment of the risk of infection associated with current generation IMID and PI-based therapy across all treatment phases will allow targeting of new approaches for prevention, early detection and treatment of infection.

2. Objectives

The aim of this systematic review and meta-analysis is to assess the effects of IMiDs and PI-based therapy on risk of infection for patients with MM at specific treatment periods: at induction (newly diagnosed), during maintenance therapy and with therapy for relapse and refractory disease.

3. Methods

3.1. Types of studies and participants

Given the primary aim of assessing the risk of infection associated with the use of IMiD or PI-based therapy compared to previously standard of care conventional therapy, phase 2 and 3 randomised controlled trials (RCTs) of IMiD or PI-based treatment regimens (single or multi agent combination) for MM were evaluated. We considered all studies which reported the following three populations of patients with multiple myeloma as defined by accepted international consensus definitions: untreated patients with newly diagnosed myeloma, patients with myeloma receiving maintenance therapy following initial treatment or ASCT and patients with relapsed or refractory myeloma.

3.2. Types of intervention/evaluation

All RCTs evaluating IMiDs or PI-based therapy for management of MM against previous standard of care therapy were eligible for inclusion. Specifically, these included:

1) IMiDs or PI-based therapies versus conventional chemotherapy as induction therapy for non-transplant-eligible patients
2) IMiDs or PI-based therapies versus combination conventional chemotherapy as induction therapy for transplant-eligible patients
3) IMiDs or PI-based therapies versus high-dose corticosteroids or placebo or interferon for maintenance therapy