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REVIEW

Changing treatment paradigms for patients with plasma cell myeloma: Impact upon immune determinants of infection

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ABSTRACT

Plasma cell myeloma (PCM) is increasing in prevalence in older age groups and infective complications are a leading cause of mortality. Patients with PCM are at increased risk of severe infections, having deficits in many arms of the immune system due to disease and treatment-related factors.

Treatment of PCM has evolved over time with significant impacts on immune function resulting in changing rates and pattern of infection. Recently, there has been a paradigm shift in the treatment of PCM with the use of immunomodulatory drugs and proteasome inhibitors becoming the standard of care. These drugs have wide-ranging effects on the immune system but their impact on infection risk and aetiology remain unclear.

The aims of this review are to discuss the impact of patient, disease and treatment factors on immune function over time for patients with PCM and to correlate immune deficits with the incidence and aetiology of infections seen clinically in these patients. Preventative measures and the need for clinically relevant tools to enable infective profiling of patients with PCM are discussed.

1. Introduction

Plasma cell myeloma (PCM) is a clonal plasma cell malignancy that is increasingly diagnosed in ageing populations [1]. In the developed world, the incidence of newly diagnosed PCM is approximately six to eight cases per 100000 population and this is projected to increase with 4700 new cases per year in the United Kingdom alone [2,3]. Infections are the most common cause of morbidity and early mortality, with an estimated 45% of early deaths due to infection [4–7]. Early infection rates are 4.68 infections per patient year with almost 30% being fatal [8]. In patients with PCM, patient age, disease and its treatment contribute to infection risk [9].

Disease burden contributes significantly to risk of infection, as demonstrated by the decreasing incidence of infection following favourable disease response to treatment [5,10]. Treatment also contributes to infective risk and as treatment regimens for PCM have evolved, so has the epidemiology of infections and factors mediating infective risk [5,11,12]. The current treatment paradigm involves the use of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PI) in combination with dexamethasone, high dose therapy (HDT) and autologous haematopoietic cell transplantation (AutoHCT) if suitable, followed by consolidation, and maintenance of disease response with IMiDs and PI [13]. With inevitable disease progression, treatment phases are repeated to obtain and maintain disease response.

PCM remains largely a disease of the elderly with a median age of onset of 70 years [14]. Increasing age is associated with functional and physiologic decline and an increased risk of infections [15]. Whilst overall survival in patients with PCM has increased, this improvement in survival has largely occurred in younger patients (below age 70). This is likely to due the impact of novel therapies and better supportive care, in particular for non-infective complications [16]. As infections are a leading cause of morbidity and mortality, it is likely that general advances in anti-infective management have also contributed to improved outcomes but the role of specific interventions such as anti-infective prophylaxis in increased patient survival remains undefined. International supportive care guidelines for patients with PCM make limited recommendations about anti-infective management and use of prophylaxis due to paucity of sufficiently robust studies [17].

Improved survival in younger newly diagnosed patients has resulted in an increasingly large population of patients maintained by multiple

Abbreviations: MHC, major histocompatibility complex; NK, natural killer; DC, dendritic cell; Th, T helper cell; TCR, T cell receptor; AutoHCT, autologous haematopoietic cell transplantation; IMiDs, immunomodulatory drugs; FN, febrile neutropenia; MDI, microbiologically documented infections; HSV, herpes simplex virus; VZV, varicella zoster virus.

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lines of treatment with cumulative immunosuppression [18]. This impacts upon the type and pattern of infections seen, including the emergence of opportunistic infections such as cytomegalovirus (CMV) and invasive fungal infections (IFI) [19–24].

The objectives of this review are to evaluate the impact of patient, disease and treatment factors on immune function over time for patients with PCM and to correlate immune deficits with the incidence and aetiology of infections seen clinically in patients with PCM. Anti-infective preventative measures and the need for clinically relevant tools to enable infective profiling of patients with PCM are discussed.

2. Host immune deficits

2.1. Age-related immunological changes and infection risk

Age, together with functional status and reserve are the determinants of suitability for HDT and AutoHCT [13]. New data suggest that older patients not receiving HDT are beginning to experience improvements in survival rates with earlier use of novel agents, narrowing the gap with an age, sex-matched general population [25]. However, overall survival rates in older patients not receiving HDT remain below those of younger patients and excess mortality is up to 3 times greater [16,25]. Therefore age remains an important determinant of prognosis in patients with PCM.

Age is also a significant risk factor for infection. Infections in the elderly occur more frequently, present atypically and are associated with poorer outcomes compared to infections in younger patients [15,26,27]. Urinary tract and the respiratory tract are leading sites of infection, and a greater diversity of pathogens is responsible for infections in the elderly [15,26,28]. Age-related immune dysfunction ('immunosenescence'), and decline of host anatomical and physiologic function contribute to risk [15,26]. Specific predispositions include breakdown of physical barriers to infection, reduced pathogen clearance by mucociliary action, loss of reflexes and impaired gastrointestinal function [26].

Immunosenescence is characterised by a shift in immune cell phenotype and decline in function with age rather than a reduction of the absolute numbers of effector cells [27]. With ageing, the numbers of neutrophils and macrophages, components of the innate immune system, are preserved but vital functions, such as chemotaxis, phagocytosis and intracellular pathogen killing, are reduced (Fig. 1) [29]. NK cell cytotoxic killing is reduced but compensated for by increased numbers with ageing [27]. Macrophages and dendritic cells have reduced antigen-presenting function [29].

In the adaptive immune system, T and B cell phenotypes are changed as a result of a shift from production of lymphoid to myeloid lineage by haematopoietic stem cell precursors and age-related involution of the thymus [30]. Consequently, there is reduction in naïve T cells (CD3+CD45RA+ cells), accompanied by an increase in mature antigenically-selected memory T cells (CD3+ CD45RO+) to maintain immune homeostasis [30–32]. This phenotypic shift occurs earlier with CD8+ T cells and is subsequently followed by CD4+ T cells and is partially due to the immune control of chronic viral infection by CD8+ memory cells [30–32]. The accumulation of memory cells results in an overall reduction of T cell repertoire in favour of previously encountered antigens and reduces the ability of the immune system to respond to new distinct antigens (Fig. 1). Immunosenescence accounts for impaired antibody responses to vaccination and its reduced efficacy in the elderly [33].

3. Disease-related immune deficits and risk of infection

In patients with PCM, a state of immune paresis is mediated by the release of cytokines TGF-β, IL-6 and IL-10 through the interactions of malignant plasma cells with the stromal cells in the bone marrow [14,34–36]. Deficits occur in all major arms of the immune system.

3.1. Innate immune system: Disease impact on monocytes and NK cells

Genetic polymorphisms of components of the innate immune system such as wild-type mannose-binding lectin genotype and myeloperoxidase promoter gene can influence risk of infection in patients with PCM [37,38]. Several key components of innate immunity are dysfunctional in patients with PCM. Critical anti-infective monocyte functions such as chemotaxis, phagocytosis and killing of pathogens are constitutively impaired and further inhibited by high paraprotein levels [39]. Treatment of PCM with resulting decrease in paraprotein results in some recovery of monocyte function [39]. Impaired pathogen clearance is compounded by failure to activate complement (C3), with both the classical and alternative pathways affected [40]. These impairments to opsonisation, phagocytosis and killing lead to an increased risk of bacterial infection (Fig. 2). Increased risk of severe infections with encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, is a result of monocyte dysfunction, deficits in complement activation, opsonisation and hypogammaglobulinaemia in patients with PCM [41]. Untreated patients with PCM may present with severe life-threatening infections or recurrent episodes of infection, most commonly due to *S. pneumoniae* pneumonia or bacteraemia [41–43].

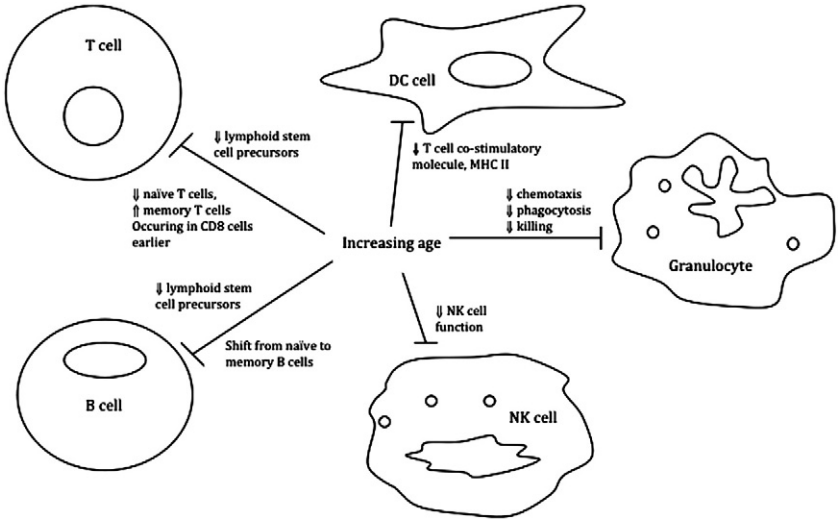

Fig. 1. Impact of increasing age on cell-mediated, humeral and innate immunity.