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Brief Communication

Potential Use of Haematopoietic or Mesenchymal Stem Cells in the Treatment of Immune Mediated Neutropenia in Domestic Canines

Arun HS Kumar

ABSTRACT
In domestic canines, neutrophils are the major component of white blood cells, which when reduced in numbers (neutropenia) can significantly compromise innate immune physiology. Several conditions are known to cause neutropenia in canines, however when neutropenia is observed without any underlying cause, it is suspected to be immune mediated neutropenia (IMN). Although IMN is treated symptomatically using immunosuppression therapy, the recent developments in stem cell therapies offer therapeutic potential especially in IMN cases which relapse. This brief report outlines the merit of haematopoietic (HSC) and/or mesenchymal (MSC) stem cells in the treatment of IMN in domestic canines. The known efficacy of HSC to repopulate the stem cell niche responsible for production of neutrophils in bone marrow together with the immunomodulatory properties of MSC can be therapeutic against IMN. Such innovative stem cell based therapies for IMN in domestic canine's merits clinical evaluation.
Key words: Neutropenia, Stem cell disease, Autoimmune, Myeloid cells, Cell therapy.

BACKGROUND

Neutrophils are the major components of the white blood cells which play very vital roles in regulation of physiology and pathology.[1] Neutrophils are often the first responders to any tissue injury where they initiate damage control and trigger early repair process thorough several paracrine and autocrine mechanisms.[1] The production of neutrophils is a very dynamic process occurring in the bone marrow under the regulation of granulocyte colony stimulating factor (G-CSF) from myeloblasts derived from the common myeloid progenitor cells.[1-3] Due to their very short lifespan of 1 to 6 days, neutrophils should be continuously produced in bone marrow to maintain their optimal levels necessary for regulation of innate immune physiology.[1,3-5]

Neutropenia and immune mediate neutropenia in domestic canines

Several conditions are known to reduce the number of neutrophils in the blood circulation, which is referred to as neutropenia.[6-10] In canines, inflammation and infections (usually non-bacterial) are the major responsible factors for neutropenia (Figure 1).[8,11] However on rare occasion (<5% of known cases) neutropenia is observed in canines with no obvious underlying conditions, which is referred to as immune mediated neutropenia (IMN).[6,8-10] Often the confirmatory diagnosis of IMN (after several expensive diagnosis approach) is based on clinical haematology showing neutropenia, absence of known causes of neutropenia and its rapid recovery (with in 3-4 days) following immunosuppression treatment.[8-10] Nevertheless IMN remains a versatile disease to diagnose. Most clinical cases of canine IMN are presented with lethargy and poor appetite with no obvious underlying conditions. The typical symptoms and treatment adopted for IMN are summarised in Figure 2.[5,6,8-10] The pathophysiology of IMN is not well known, however it is reported that the autoantibodies generated against selective targets on neutrophils result in their phagocytosis and hence their selective elimination from blood circulation eventually leading to neutropenia. However neither the nature of these autoantibodies nor the neutrophils markers which are targeted by the immune system are well characterised.[4,6-8] Although most canines with IMN recover following short term immunosuppression therapy, however there are reports of regular reoccurrence of IMN as well.[8,11] In cases with IMN relapse, the long term immunosuppression may potentially be associated with several undesirable outcomes. Hence there is need to look at safe, reliable, and efficient alternative options to treat in canine IMN patients.

Potential role of haematopoietic/ mesenchymal stem cells in therapy of IMN

The specific incidence of the IMN reoccurrence, calls it to question if IMN is a stem cell disease? i.e.,

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Arun HS Kumar, DVM, PhD
School of Veterinary Medicine, University College Dublin, Belfield, Dublin, IRELAND.

Correspondence
Dr Arun HS Kumar, DVM, PhD
Stemcology, School of Veterinary Medicine, University College Dublin, Belfield, Dublin-04, IRELAND.
Phone no: 0035317166230
E-mail: arun.kumar@ucd.ie

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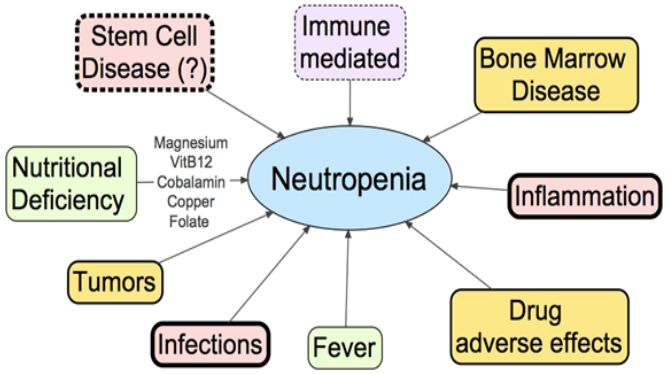

Figure 1: Potential causes of neutropenia in canines.

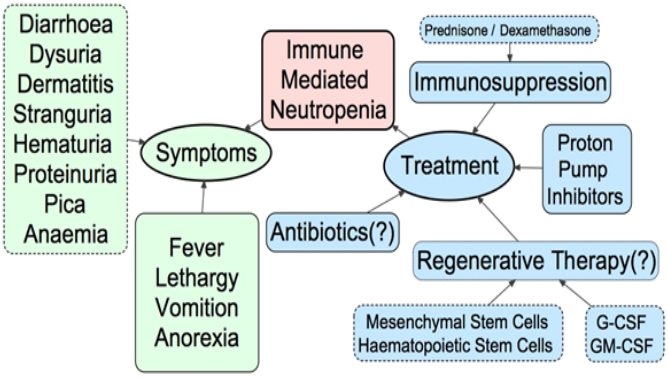

Figure 2: Symptoms and treatment of canine immune mediated neutropenia.

a disease associated with defects in or poor functioning of the stem cell responsible for continuous production of neutrophils. A detailed understanding of this hypothesis will requires first defining the nature of stem cells responsible for production of neutrophils in canines.[2,12] In humans the common myeloid progenitors are defined by the expression of CD34 and CX3CR1 cell surface markers.[2,12] Additionally expression of CD117, CD33, CD56, CD5 and CD7 markers is also reported. It remains to be seen if these markers are relevant to define common myeloid progenitors in most breeds of canine species as well. Establishing these basic science facts using well established stem cell screening techniques will pave the way for developing stem cell based therapies for IMN in canines especially in the patients where frequent relapse of IMN is observed.[2,12] In this contest based on our extensive knowledge of stem cell therapies in humans, haematopoietic stem cells (HSC; CD34 positive cells) or mesenchymal stem cells (MSC; CD73, CD90, CD105 positive cells with osteoblasts, adipocytes and chondroblasts differentiation potential)[2,12] may find application in the therapy of IMN in canines (Figure 2). Considering the pivotal role of G-CSF in the regulation of myeloid stem cells, clinical strategies to test the efficacy of HSC and/or MSC in combination with G-CSF merits evaluation. The co-administration of MSC together with HSC may be required as recent metanalysis of using HSC in humans have indicated the stem cells induced cytopenia as a potential side effect,[2] in which the well-established immunomodulatory efficacy of MSC will be beneficial. Although in my opinion the observation of cytopenia following HSC therapy is possibly due to poor stem cell therapy practices rather than a direct effects of the stem cells. Several HSC therapy based clinical trials have convincingly established the safety of these cells for clinical use. The wider availability of techniques to quickly isolate and make available adequate amount of HSC for clinical use should merit the use of these stem cell therapies to evaluate their efficacy in improving clinical cases of IMN in canines.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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