



Review

Cancer chemotherapeutics in rheumatoid arthritis: A convoluted connection

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ABSTRACT

Chemotherapy is one of the most popular therapeutic strategies to treat cancer. However, cancer chemotherapeutics have often been associated with impairment of the immune system, which might consequently lead to an augmented risk of autoimmune disorders, such as rheumatoid arthritis. Though the accurate mechanistic facets of rheumatoid arthritis induction have not been interpreted yet, a conglomeration of genetic and environmental factors might promote its etiology. What makes the scenario more challenging is that patients with rheumatoid arthritis are at a significantly elevated risk of developing various types of cancer. It is intriguing to note that diverse cancer chemotherapy drugs are also commonly used to treat symptoms of rheumatoid arthritis. However, a colossal multitude of such cancer therapeutics has demonstrated highly varied results in rheumatoid arthritis patients, including both beneficial and adverse effects. Herein, we attempt to present a holistic account of the variegated modalities of this complex tripartite cross-talk between cancer, rheumatoid arthritis and chemotherapy drugs in order to decode the sinuous correlation between these two appalling pathological conditions.

1. Cancer, chemotherapeutics and rheumatoid arthritis: A tripartite functional axis

About seventy percent of the global deaths are attributed to non-communicable diseases, among which cancer is a forerunner [1], causing millions of deaths every year [2]. This necessitates development of relevant strategies to encounter the colossal morbidity and mortality associated with the ailment [3,4]. Chemotherapy, the most preferred mode of intervention against cancer, exhibits significant clinical benefits [5–8]. However, several side effects (neurosensory disorders, obesity, cardiovascular diseases, infertility, etc.) often make its administration a risky endeavor [9–11].

Among adverse effects, chemotherapy is also associated with anomalies of the immune system, which augment risks of infections or a frail immunity [12–15]. On this note, it is pertinent to focus on autoimmune disorders (ADs), which are a group of diseases of the immune system that have emerged with enormous prevalence in the present decade [16]. The normal immune system recognizes all antigens (except autoantigens) as ‘foreign’ and mounts a response against them [17–19]. This is implemented by regulatory cross-talks between a multitude of specialized components (macrophages, lymphocytes, cytokines, antibodies, etc.) [20,21]. A defect in any of them can lead to autoimmunity – the cognition of ‘self’ as ‘foreign’, which inadvertently

leads to ADs (like Hashimoto’s thyroiditis, systemic sclerosis, systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis (RA), etc.) [22–28].

RA is one of the most common ADs [29], which levies an immense cost on health expenses [30,31]. It is characterized by synovial and systemic inflammation, bone and cartilage destruction, and high levels of autoantibodies, particularly rheumatoid factor (RF) [32–34]. Based on its etiology, RA can be: (i) refractory (patient fails to achieve remission even after treatment) [35]; (ii) seropositive or seronegative (presence or absence of RF respectively) [36] and (iii) juvenile idiopathic arthritis (onset in children and adolescents below sixteen years) [37]. Though the precise trigger for RA manifestation has not been deciphered, diverse genetic and environmental factors (such as imbalance between interleukin-1 (IL-1)/IL-1 receptor antagonist (IL-1Ra) [38,39], perturbed distribution of Th17 and Treg cells [40], and VEGF-mediated hyperplasia [41]) interact with each other to holistically determine the etiology of RA [42,43].

What makes RA more challenging is its prominent risk of comorbidity (occurrence of other diseases) that, in turn, augments mortality rate [44]. RA patients are at an elevated risk of cancer [45–47]. In a cross-sectional study, 21.4% (out of 11,782) of the subjects with RA were found to have coincident instances of cancer [48]. The current RA therapeutic regimen uses drugs that are non-steroidal anti-

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inflammatory drugs (NSAIDs); analgesics; corticosteroids or disease-modifying anti-rheumatic drugs (DMARDs) [49–53]. DMARDs can be biologics like rituximab (Rtx) [31], infliximab [54] or non-biologics like methotrexate (Mtx) (a cancer chemotherapeutic and interestingly, the primary treatment strategy for RA) [31,55,54] and leflunomide [56]. Biologic DMARDs are artificially engineered drugs that target (i) cytokines; (ii) inflammation inducing cells, etc. [49], whereas non-biologic DMARDs alleviate pain and prevent irreversible damage [57]. In addition to these, certain putative cancer chemotherapeutics such as cyclophosphamide (Cpm) [58,59], etoposide [60], prednisone (Pdn) [61], melphalan [62,63], paclitaxel [64] and procarbazine [65,66] have also been administered to combat RA. While none of them could completely cure RA *per se*, side effects concomitant with cancer chemotherapy were reported [67–69]. Thus, prescribing these drugs solicits thorough consideration of both the target and the treatment. In the light of this predicament, this review focuses on the myriad effects of cancer chemotherapy drugs as potent RA therapeutics, particularly highlighting their beneficial and/or deleterious outcomes. We attempt to fathom the effects of these drugs (either in monotherapy or in combination) in RA patients, and also in patients with coincident RA and cancer. The elucidation of the tripartite cross-talk between cancer, RA and chemotherapy drugs might enhance our understanding of the complexities involved in the modalities of treating the two dreaded ailments.

2. Effects of cancer chemotherapeutics in RA patients

2.1. Mustard gas derivatives

Mustard gas derivatives, a putative group of cancer chemotherapeutics, produce a conflicting array of results in RA patients. In a case study, administration of mechlorethamine (HN2) to an RA patient exhibited a drastic depletion in T lymphocytes (especially memory T cells), thereby improving his condition by reducing pain and stiffness [70]. Cpm, another mustard gas derivative [71], demonstrated mixed results. A seventy two-year old RA patient with rheumatoid vasculitis was cured with an induction treatment of high dose corticosteroid and Cpm, followed by a maintenance treatment [72]. In another case of seronegative RA and rheumatoid vasculitis, toxic epidermal necrolysis occurred upon treatment with Cpm and mesna [73]. Methylprednisolone and Cpm combination therapy to a fifty four-year old RA patient with multiple rheumatoid bursal cysts led to remission during a six month follow-up [74]. In other patients, Cpm completely failed to treat vasculitis lesions [75,76]. Interestingly, Cpm administration in RA patients is also associated with incidences of leukemia, myelotoxicity, sterility and increased risks of chronic kidney diseases [77,78].

Chlorambucil, a mustard gas derivative that is sold under the brand name Leukeran® [79], exhibits deleterious effects similar to those seen in Cpm-based treatment strategy [77,80]. However, despite its adverse effects, chlorambucil has been proven to be effective against amyloid A (AA) amyloidosis (AAA) in juvenile RA [81,82]. It also significantly decreases proteinuria in patients with renal amyloidosis, which is a condition associated with RA. It is to be noted that this reduction in proteinuria occurs only when the drug is administered before the complete loss of renal function [83]. Chlorambucil has also been reported to have caused a marked regression in nephrotic syndrome in a twenty two-year old RA patient who had been previously subjected to gold and penicillamine (breakdown product of penicillin [84]) regimens that had eventually triggered the syndrome [85]. While overdose of chlorambucil has depicted contraindication (leukopenia and renal dysfunction) in several patients, appropriate doses have enhanced complete recovery from AAA [86]. Despite its significant improvements in the conditions of several RA patients, administration of chlorambucil is still challenging as it is often associated with an increased risk of leukemia, cutaneous and haematological neoplasms [87]. It has particularly been imputed as one of the chief reasons for development of leukemia in children with juvenile RA [88].

Two more mustard gas derivatives, melphalan and thiotepa, have also exhibited contraindications when used to treat RA. Melphalan introduces chromosomal anomalies and also increases the risk of acute leukemia in RA patients [62]. Also, in a case study, a fifty seven-year old Japanese woman diagnosed of RA was cured when treated with high dose melphalan in combination with autologous stem cell transplantation, but reported a relapse after three years [89]. Thiotepa, a chemotherapeutic alkylating agent [90,91], when administered to RA subjects, showed severe morbidity, reduced overall functional capacity, lowered grip strength, clinical deformity and work disability [92,93].

2.2. Folate antagonist: Mtx

Folate (a member of the vitamin B family) metabolism is vital for DNA replication in cancer cells – a property that is targeted by folate antagonists, thereby making them a preferred group of cancer chemotherapeutics [94]. Mtx is a widely explored and commonly used (either in monotherapy or in combination) folate antagonist [95,96], which in fact is the most crucial module of RA therapy [97–99]. Upon entering cells, Mtx gets converted to polyglutamate forms that are capable of inhibiting dihydrofolate reductase and other folate-dependent enzymes like 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, thereby ultimately depleting reduced folate in the cells [100]. Accumulation of AICAR subsequently pushes the anti-inflammatory agent adenosine out of the cell [100]. Furthermore, Mtx significantly reduces serum IL-8, IL-1B, TNF α and IL-6 [101,102]. Thus, Mtx administration mitigates inflammation and subsequently establishes its efficacy in RA patients [100,103,104]. Low doses of Mtx have been demonstrated to suppress the JAK/STAT pathway, which is suggested to be the main immunosuppressive and anti-inflammatory mechanism of the drug at low doses [105]. In a recent study, it was established that repeated intra-articular Mtx administration in RA patients decreases joint synovitis of medium-sized joints [106]. Patients in early stages of RA, when treated with Mtx, depicted truncated levels of serum uric acid and reduced number of swollen joints [107]. Mtx treatment in RA patients has also been associated with lower cardiovascular risk compared to treatment with other DMARDs [108,109]. The drug activates AMPK-CREB pathway, thereby protecting from cardiovascular anomalies by conditioning the endothelium [110,111]. Another study has corroborated these results by stating that Mtx might prevent increase in blood pressure (BP) caused due to arterial stiffness in RA patients [112]. This may allude to the fact that Mtx-treated RA patients have significantly reduced BP compared to non-Mtx subjects [109]. Also, Mtx (when treated alongwith low-dose prednisolone) was shown to enhance adiponectin levels, which in turn mitigates insulin resistance, thereby having favourable effects on the cardiovascular system [113]. Implementation of the 2010 ACR/EULAR (American College of Rheumatology/European League against Rheumatism) RA classification criteria (which suggested administration of higher doses of Mtx supplemented with lower doses of Pdn) has demonstrated significantly augmented rates of remission [114]. Hypomethylation of DNA occurs in RA patients, which was observed to be reversed by the drug [115]. Mtx is also the first-line therapy to treat pseudo Felty's syndrome (PFS), which is an uncommon condition coincident with RA (distinguished by neutropenia and monoclonal expansion of lymphocytes) [116].

However, inspite of its multiple beneficial effects, Mtx has been reported to induce several side effects as well (Fig. 1). In fact, while low doses of Mtx are anti-inflammatory in nature, higher doses are anti-proliferative and cytotoxic [117]. In a fifty two-year old woman with RA, chronic treatment with low doses of Mtx resulted in osteopathy due to inhibition of osteoblast proliferation, and consequently retarded bone formation and caused osteopenia [118]. A seventy one-year old RA patient developed symptoms of dysautonomia, which worsened due to Mtx therapy. Discontinuation of Mtx and treatment with leflunomide achieved remission of the RA symptoms [119]. In fact, presentation of

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