Immunosuppressive agents in hematopoietic stem cell transplantation

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Abstract

Hematopoietic stem cell transplantation has been used in many malignant and non-malignant diseases successfully. Allogeneic stem cell transplantation has its own immunologic characteristics such as graft versus host disease. In order to prevent graft versus host disease, immunosuppressive medications are required. Immunosuppressive drugs have diverse mechanisms of action thus they could be used in different clinical status. Steroids and methotrexate are nonspecific; cyclosporine, tacrolimus, sirolimus and mycophenolate are T cell specific immunosuppressive drugs. Antibodies, monoclonal antibodies, and new drugs such as ruxolitinib are available treatment options but we still need improvement and innovation in management of graft versus host disease.

Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment modality for a wide range of malignant and non-malignant diseases. Immunosuppressive treatment is required following allogeneic hematopoietic stem cell transplantation (allo-HSCT) in order to prevent graft versus host disease (GVHD) and associated organ-tissue lost. Donor T cells recognize different histocompatibility antigens of the host cells as foreign. As a result of antigen recognition, activated Tcells secrete cytokines such as interleukin (IL) -1, IL-2, tumor necrosis factor (TNF), and gamma-interferon, so that GVHD process begin [1]. GVHD is classified as acute and chronic according to time of onset. Classically acute GVHD occurred within 100 days after transplantation. Rarely, patients may present acute GVHD findings after than 100 days which is named 'persistent, recurrent, late onset acute GVHD'. 'Overlap syndrome' is another clinical scenario which may carry both acute and chronic GVHD features at any time after HSCT [2]. Numerous risk factors have been identified for development of acute GVHD, one of the most important one is acute GVHD prophylactic regimen used [3]. Immunosuppressive agents for prophylaxis and treatment of GVHD are evaluated in two major categories: 1- Non-specific immunosupressives, 2- T cell mediated drugs, 3- Antibodies, 4- Other drugs.

Non-specific immunosuppressive drugs

a-Corticosteroids: Although mechanism of action is not fully understood, corticosteroids are agents that are preferentially used and combined with other immunosuppressive in acute GVHD treatment. Corticosteroids are thought to reduce T cell numbers, diminish expression and production of inflammatory cytokines such as IL-1 and TNF alfa (1), and inhibits cytokine gene transcription [4].

In acute GVHD treatment, intravenous methylprednisolon is preferred because patients may not be able to take oral medication or there may be malabsorbtion because of severe mucositis. If oral medication is available oral methylprednisolone or rarely oral prednisone can be prescribed.

The classical, first-line treatment in acute GVHD is methylprednisolone. It should be initiated if GVHD is grade 2 or higher and initilal dose is 2 mg/kg/day given in two divided doses. Initial dose is recommended to be continued for 7 days. Tapering strategy is based on the clinical response and it should not be stopped until all signs of GVHD are disappeared. In gastrointestinal GVHD, oral budesonid may be given synchronous with methylprednisolone [5].

Methylprednisolon is preferred in GVDH prophylaxis in combination with other immunosuppressive drugs. Adding steroid provides reducing immunosuppressant-related toxicity without altering the efficacy [6].

Corticosteroids have several side effects such as making susceptibility to infections, Cushingoid appearance, psychosis, hyperglycemia, hypertension, osteoporosis, bone aseptic necrosis, and cataract formation.

b-Methotrexate: Methotrexate is a folic acid antagonist and inhibits dihydrofolate reductase (DHFR) which converts folic acid to reduced tetrahydrofolate. Tetrahydrofolate transfers single carbon groups which are used for purine and thymidylate synthesis [7]. Eventually, methotrexate prevents nucleotide synthesis. Lymphocytes are relatively more prone to methotrexate because intracellular polyglutamate formation is more prominent in lymphocytes which is toxic for DHFR and augments antifolate activity [8]. In GVHD prophylaxismethotrexate is thought to reduce activated T cell proliferation.

The most common side effects are renal, gastrointestinal, and hepatic toxicity. In patients with renal failure, methotrexate may be more toxic and dose reduction is necessary. If a there is a fluid collection (ascites, pericardial or pleural effusion) in any part of the body, methotrexate should not be administered because the increased risk of acute renal failure.

Methotrexate classically administered intravenously on days +1, +3, +6 and +11after allo-HSCT, in combination with cyclosporine [9].

Specific T cell immunosuppressive drugs

a-Cyclosporine: It is a calcineurin inhibitor that is extracted from fungi, blocks the transcription of cytokine genes in activated T cells. Cyclosporin makes a complex with cyclophilin, inhibits the phosphatase activity of calcineurin which regulates nuclear translocation and activation of NFAT (nuclear factor of activate T cells) transcription factors. Furthermore, cyclosporine blocks the activation of JNK (Jun N-terminal kinase) and p38 signaling pathways triggered by antigen recognition, making cyclosporin a highly specific inhibitor of T cell activation [10]. The analogous cytosolic protein for the drug tacrolimus is FK binding protein (FKBP). Both cyclophilin and FKBP function as the enzyme prolylcis-trans isomerase (another name rotamase) [11]. Rotamase takes part in protein folding process. Inhibition of rotamase by cyclosporin and tacrolimus is thought to be important step in immunosuppression.

Major side effects are nephro and hepatotoxicity, hypertension, hyperglycemia, headaches, hirsutism, gum hypertrophy, brittle nails, acne, nausea, vomiting, neurotoxicity, and thrombotic microangiopathy. Nephrotoxicity is dose related and associated with vasoconstriction and ischemia of the afferent arterioles in the kidney [12,13]. It should be kept in mind that there may be interactions between cyclosporine and drugs metabolized by cytochrome p450 enzymes such as voriconazole.

In myeloablative conditioning regimens, the standard GVHD prophylaxis is cyclosporine and short course of methotrexate. The initial cyclosporine dose is 3 mg/kg/day starting on the preceding the infusion of the stem cells (day -1). It is given as short intravenous bolus, preferably in two divided doses. If oral intake is available, we can change the route by giving the first oral dose twice of the last intravenous dose. Dose adjustment is necessary according to blood drug concentration and toxicities. The target cyclosporine concentration is 200–300 mg/L during the first 3–4 weeks, then 100–200 mg/L until 3 months after transplantation if there is no GVHD or toxicity. Drug concentration should be measured after 12 hours from administration. Prophylaxis is continued until 6 months if GVHD is absent. Tapering the dose is possible after 3 months in the absence of GVHD [5]. Cyclosporine prophylaxis regimen is the same in reduced intensity conditioning allo-HSCTs.

b- Tacrolimus (FK506): Mechanism of action, administration, and clinical use are quite similar to cyclosporine. Major side effects are neuro and nephrotoxicity, hyperglycemia, dyspnea, musculoskeletal pain, anorexia, nausea, vomiting, abdominal pain, itching, fatigue, and thrombotic microangiopathy. Central nervous system effects are in wide spectrum such as headaches, tremors, paresthesias, seizures, photophobia, mental status changes, mutism, and encephalopathy [14].

Cyclosporine and tacrolimus are accepted as equivalent in GVHD prophylaxis, but the latter is less frequently used and experienced in Europe [5].

Its dose in GVHD prophylaxis is 0.03 to 0.04 mg/kg per day as a continuous infusion. When oral intake is available 0.15 mg/kg per day administered in two divided doses. The target blood concentration is 10 -30 ng/mL.

c-Sirolimus: Sirolimus (rapamycin) is a macrolide that is currently approved by the FDA only in solid organ transplantation in order to prevent organ rejection.

d-Mycophenolate: There are two forms available: 1-Mycophenolate mofetil (MMF): Morpholinoethyl ester of mycophenolic acid (MPA), 2- Sodium salt of mycophenolate. MMF is a prodrug of MPA, which is an inhibitor of inosine monophosphate dehydrogenase. This enzyme is rate-limiting in de novo synthesis of guanosine nucleotides. T and B lymphocytes are more dependent on de novo pathway than other cells [15].

Major side effects are neutropenia, hyper or hypotension, abdominal pain, hyperglycemia, and nephrotoxicity.

The standard GVHD prophylaxis in reduced intensity conditioning regimen is cyclosporine and MMF combination. The standard dose is 30 mg/kg/day, orally, in two divided doses. Administration is started on day +1 and continued. Dose adjustment according to toxicity is required. Treatment should be continued 1 month in sibling transplantations, 3 months in unrelated or mismatched donor transplantations [5].

Antibodies

a- Antithymocyte Globulin (ATG): It is a polyclonal immune globulin can be produced by injection of thymocytes to horses or rabbits, and by using Jurkat cells as an antigen. Because of the polyclonal nature of ATG, has diverse effects on the immune system. ATG makes complement mediated T-cell depletion, modulates surface molecules of the leukocytes and endothelial cells, stimulates B cell apoptosis, changes dendritic cell functions, and induces regulatory T cells and natural killer cells [16].

ATG is recommended in GVHD prophylaxis of unrelated donor transplantations either in myeloablative or non-myeloablative regimens. Doses of two different brands are: ATG-Frensius is 10 mg/kg for 3 days (total dose 30 mg/kg) and Thymoglobulin is 2.5 mg/kg for 3 days (total dose 7.5 mg/kg), both administered on days -3, -2, and -1. ATG may also be used in treatment of acute GVHD as a second-line treatment [5].

Other drugs

a-Rituximab: Adding anti CD-20 monoclonal antibody rituximab into preparative regimens or chronic GVHD treatment protocols is thought to suppress donor B cell immunity. At present, rituximab is not standard drug in HSCT era. It may be an option in second-line chronic GVHD treatment.

b-Ruxolitinib: A selective Janus kinase (JAK) 1/2 inhibitor ruxolitinib is an oral drug used in myelofibrosis treatment, have recently been discovered to be beneficial in acute and chronic GVHD treatment. JAK 1/2 takes place in multiple steps in GVHD related inflammation and tissue damage such as T cell activation, lineage formation and survival through the common gamma chain of six different interleukins (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) [17], activation of neutrophils [18], and dendritic cells [19].

A recent, large multicenter study pointed that ruxolitinib has high response and 6-month survival rates in steroid refractory acute and chronic GVHD patients [20].

Anti tumor necrosis factor agents, extracorporeal photopheresis, and mesenchymal stem cell infusion are some of the alternative treatment modalities for chronic GVHD [5].

There is no standard approach in chronic GVHD treatment, therefore transplantation centers should choose the appropriate one according to their clinical practice, availability of drugs, and institutional guidelines.

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