

Cytokine release syndrome: an overview on its features and management.

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Abstract

CRS is a life threatening toxicity associated numerous immunotherapeutic techniques involving monoclonal antibodies, biospecific antibodies and adoptive T cell therapies. It is also referred as infusion reaction that results in release of large amount cytokines (Like IL-6, IFN- γ , INF) from the target cells. Cytokines when released in excessive amounts into the circulation produces systemic symptoms like nausea, shills, fever, rashes, headache, hypotension, dyspnea etc. Most of the patients present mild to moderate symptoms which can be managed easily but some patients show life threatening symptoms. Studies have shown that immunosuppressive agents like corticosteroids and tocilizumab can reverse the toxicity of CRS, however such immunosuppression may limit the immunotherapeutic efficacy. Therefore specific precautions must be considered in such patients to prevent exacerbation of the complication. Thus, this review is based on the overview of CRS which include etiology, mechanism and management of CRS, so that immunotherapeutic benefits can be maximized with minimum risk of complication.

Keywords: Cytokine release syndrome, Monoclonal antibodies, Chimeric antigen receptor modified T-cells, Corticosteroids.

Accepted on February 12, 2019

Introduction

Treatment of various disorders whether malignant or non-malignant via use of monoclonal antibodies or adoptive therapy using modified T cells, have now evolved as a fundamental part in clinical practices. However, such treatment regimen can also result in serious and fatal outcomes, one of which is described as cytokine release syndrome (CRS) [1].

Cytokines, the chemical messengers that are protein in nature, are produced by majority of the cells in the body [2]. Some examples of cytokines are interleukins (ILs), tumor necrosis factor (TNF) and interferons (IFNs). Broadly cytokines may be categorized as monokines, lymphokines and chemokines. Cytokines of macrophages or monocytes origin are called monokines while cytokines that originate from lymphocytes are termed as lymphokines. Similarly the cytokines that attract immune effector cells to the targeted area by binding on to the target cells are known as chemokines [1].

- Cytokines perform various functions in the body. Some of them are as follows:
- Assist in cell to cell communication
- Involved in hematopoiesis
- Regulate the functions of both innate and acquired immune system and also coordinate their responses with various organs [2].
- Stimulate or inhibits cellular growth

- Activate lymphocytes or other immune effector cells
- Stimulate degradation of monoclonal antibody targeted cells
- Stimulate inflammatory responses [1].

Cytokines exhibit regulatory functions similar to that of hormones; however they are distinct from hormones with regards to pleiotropic function and redundant nature [2]. They are important in host defense and tissue homeostasis but abnormally high level can cause acute and chronic impairments, one of the known examples being cytokine release syndrome (CRS). CRS was unknown till 1990s when it was observed in the patients whom muromonab CD3 (anti-mouse monoclonal antibody) was administered to treat allograft rejection [3]. After this several other antibodies associated with CRS were identified such as chimeric rituximab (anti-CD20), humanised alemtuzumab (anti-CD 52), TGN1412 (CD 28 agonist) [4], obinutuzumab [5], brentuximab [6], dacetuzumab [7] and nivolumab [8]. Besides these non-protein anti-cancer agents like lenalidomide [9] and oxaliplatin [10] are also reported to develop CRS following their administration. Other contributing factors to CRS development include graft versus host disease, haploidentical stem cell transplantation and massive T-cell stimulation [11].

CRS is a cytokine associated toxicity that results from excessive immune activation. Immune activation is the basic mechanism underlying modern immunotherapies in order to

attain desired clinical benefit. However, activation of immune system by immunotherapeutic agents beyond the normal results in the flooding of cytokine and adverse effects. Since immunotherapeutic techniques are becoming trendier in the recent times, the prevalence of CRS is also increasing [12].

The recent picture of immunotherapeutic techniques shows the increasing use of T-cell based immunotherapeutic agents due to their higher success rate. However, with the success of such T-cell engaging therapies, the concerns regarding CRS also has been growing side by side, since it is one of the most frequently observed health hazards of these types of therapies. T-cell based immunotherapeutic approach includes infusion of bispecific antibodies such as blinatumomab (used in leukemia) [13], haploid mononuclear cells (used in refractory leukemia) and adoptive immunotherapeis (use of genetically engineered T-cells that express chimeric antigen receptors, CART) [14].

Symptoms

Symptoms associated with CRS in most of the patients are mild (flu, fever and myalgias) while they may be severe in some patients. The severe inflammatory syndromes include hypotension, vascular leak, pulmonary edema, coagulopathy and multiple organ system failure. The details of symptoms and sites of body affected are shown in Table 1. Recently CRS induced death has also been reported after the administration of blinatumomab [15].

Time of onset of symptoms and severity of CRS depend on the drug infused, level of immune activation and burden of the disease [16]. Similarly following CART therapy, development of CRS may take few days to several weeks. The incidence of CRS after administration of conventional mAbs (monoclonal antibodies) is quite low compared to T-cell based anti-cancer immunotherapies as they pose higher risk of CRS. CD-19 targeted CART-cells and blinatumomab were the first T-cell engaging immunotherapies against hematological malignancies and have been reported to show 100% incidence of CRS following the drug administration and in some cases they were associated with fatal outcomes [17].

In case of rituximab, symptoms appear within minutes to hours after administration of drug. In some cases CRS may be followed by hemophagocytic lymphohistocytosis (HLH). Study of Grupp et al. showed that, among the patients who had undergone CD19-CART therapy, one patient was reported to have severe CRS along with HLH. The patient was found to have mutated perforin gene that is responsible for HLH development [18]. It has shed light on whether host genetic factor mediates CRS following immunotherapeis, but needs further research evidences.

Table 1. Symptoms associated with CRS and sites of body affected.

Organ systems affected	Symptoms
Constitutional	Fever, headache, anorexia, malaise, myalgias, rigors [19,20]
Integument	Skin rashes [11,19]

Blood	Cytopenias (anaemia, leucopenia, lymphopenia, thrombocytopenia), increase in D-dimer, hypofibrinogenemia [18,21]
Cardiovascular	Mild: Tachycardia with fever Severe: Hypotension, decreased cardiac output, arrhythmias, cardiac arrest [22,23]
Pulmonary	Hypoxia, dyspnea, pulmonary edema, pneumonitis, mechanical ventilation required in some cases [12,24]
Gastrointestinal	Diarrhoea, abdominal pain, colitis, hyperbilirubinemia, transaminitis [17,25]
Renal	Electrolyte imbalances, azotemia, renal injury due to reduced renal perfusion [19,23]
Nervous	Headache, confusion, hallucination, dysphasia, tremor, seizure, facial nerve palsy, altered gait [15]
Musculoskeletal	Elevated creatine kinase, myalgias, weakness [19,23]

Mechanism of CRS Development Following Immunotherapy

On administration of monoclonal antibodies

There are two basic mechanisms which describes development of CRS after therapy involving monoclonal antibodies (mAB). They are type 1 reaction and type 2 reaction. Type 1 reaction involves Fab region of mAB. Fab binds with the activation receptors present on the surface of target cells thereby leading to the generation of transduction signal and flooding of cytokines. Monoclonal antibodies such as TGN412 and muromonab act *via* this mechanism.

Incase of type 2 reaction, there is involvement of Fc region of mAB. Fc receptors present on the surface of antibody opsonised target cells bind with Fc region of antibody followed by signal transduction and massive release of cytokines. Drugs like rituximab and alemtuzumab act *via* this mechanism. An alternate mechanism has also been postulated which states that these antibodies may activate natural killer cells and cause flooding of cytokines through ligation of CD-16 [3].

T-cell engaging therapies

Genetically modified T-cells or CART: T-lymphocytes can be genetically modified to express a domain called single chain fragment variable (scFv) region. Such modified T-cells are called CART cells. The new domain scFv binds to signaling and co-stimulatory domains (CD Z8 and CD137) of T-cell receptor [17]. CART cell therapy can result in CRS by direct or indirect mechanisms. Incase of direct mechanism, the infused modified T cells directly induces the production and release of cytokines in excessive amount. Indirectly, such infused cells first secrete cytokines in response to which other immune cells like macrophages secrete large amount of cytokines [26]. T cell engaging therapies cause activation immune cascade leading to HLH/MAS in both the patients predisposed with or without known mutation in gens causing HLH [27]. The clinical and laboratory profile of CRS associated with HLH additionally

shows the presence of high blood levels of triglycerides and ferritin. In phase III study conducted by Kantarjian et al. using blinatumomab for the treatment of acute lymphoblastic B-cell lymphoma (B-ALL), signs of HLH were observed in 4 out of 13 patients [28].

Bispecific T-cell engagers: Bispecific T-cell engagers, also termed as BiTEs, are molecules developed mostly for cancer immunotherapy [29]. In BiTEs there are two single chain variable fragments (scFv) connected by a flexible linker. Of two chains, one chain links with CD3 molecule and the other binds with antigen associated tumor cells. Upon ligation T-cells are stimulated and cytokines are released that ultimately leads to tumor clearance [30]. Various BiTEs are now being developed and subjected to clinical trials to assess their efficacy and safety. Some examples are blinatumomab (MT 103), MT 110, BAY2010112 etc. [31].

Predictors of CRS

Number of clinical studies has identified several predictive factors for CRS, the common being the type of immunotherapy, underlying disease to be treated and patient features. Due to their growing application in recent years, several clinical studies have focussed on CRS severity following T-cell based therapies. As per these studies, CRS inducing drugs display the feature of 'first dose effect' which indicates that severe CRS symptoms are observed only after administration of first dose and recurrences do not persist on subsequent administration.

The cause of such first dose effect may be due to high disease burden at the initial stages of treatment [32]. Disease burden is considered one of the most important predictive factors of severe CRS outcomes following CART-cell and bi-specific T-cell therapies [33]. It has been proven clinically in murine models. On administration of CART-cells, murines having high tumor (lymphoma) burden demonstrated fatal CRS outcomes while those having low disease burden did not develop any signs of CRS [34]. Similarly dose of drug administered is another predictive factors of CRS risks [23].

CRS is more frequently observed in pediatric patients undergoing immunotherapy compared to adults. The main cause is still unknown, however hypothesis is being made that correlates such higher incidence in pediatric group with the higher dose of drug used, due to immaturity of immune system in these patients. Two clinical trial studies were conducted by Lee et al. [23] and Maude et al. [35] on paediatric patients suffering from acute lymphoblastic leukemia. In both the trials, the patients were administered CD-19-CART-cells and the incidence of CRS observed were 100% and 76% respectively.

Similarly in another two clinical trial studies involving patients having NHL (Non-Hodgkin lymphoma), the prevalence of CRS was found to be 93% on administration of CD-28-CART-cells while it was 57% with 4-1BB-CART-cells [36,37]. Moreover, it has been also reported that lymphodepletion prior to CART-cell therapy too, influences CRS severity. According to Hay et al. lymphodepletion with fludarabine and

cyclophosphamide further increases the incidence of CRS following CART-cell therapy [38].

Differential Diagnosis

In CRS, large amount of cytokines are released in circulation. However several issues are still to be addressed for effective use of such cytokine measurement to diagnose and define the severity of disorder. Some important issues are:

- Need of clinical laboratory improvement amendments (CLIA) certified assays which are not readily available in most of the hospitals.
- Prediction of severity of disorders on the basis of cytokine level is uncertain [14]
- Profiles of different cytokines are needed to be studied rather than single.
- Though number of cytokines is produced, recent immunotherapeutic practices involve inhibition of IL-6 signaling as, it is implicated to be a central mediator of CRS related toxicities [14].

Further, CRS is associated with the number of unspecific syndromes, thereby putting additional load on its diagnosis. Thus, it is very essential from the part of clinicians to elute out CRS from other disorders which share similar clinical profiles.

Tumor lysis syndrome (TLS)

The common symptoms shared by both TLS and CRS include fever, seizure, cardiac arrhythmia and renal failure. However, TLS can be easily ruled out based on the laboratory profile like hypocalcemia, hyperphosphatemia and hyperkalemia. But if there is concurrent occurrence of CRS and TLS, it rather complicates the diagnostic procedure [39].

Sepsis

Most of the patients with severe CRS display similar clinical picture required for diagnosis of sepsis, such as suspected infection associated with organ dysfunction (assessed by SOFA score also called sequential Organ Failure Assessment score) and septic shock (indicated by the elevated lactate levels along with the requirement of vasopressors), thereby making it extremely difficult to differentiate CRS from sepsis. Unfortunately, it is very important to distinguish the patients with sepsis from those with CRS since therapeutic modalities used for CRS may be lethal if applied to the patients with sepsis [40].

Infections

CRS is associated with increased risk of infection; however the underlying mechanism is still unclear. Immunosuppressive drugs are used in the treatment of CRS, thus resulting in masking of signs of infections and hence delay the diagnosis. CRS is predominantly associated with bacterial infections, followed by that of viral origin. Fungal infections, though rare in CRS, could be observed in patients who had previously received allogenic or autologous stem cell transplantation [41].

Therefore, occurrence of infection must be effectively monitored with appropriate anti-microbial therapy.

HLH/MAS

HLH/MAS is manifested as a part of severe CRS. It is difficult to diagnose HLH associated CRS from primary HLH and other conditions mimicking the symptoms of HLH such as sepsis. Though HLH/MAS in most cases occur concurrently with CRS, It is necessary to rule out other probable causes of HLH, i.e. genetic disorder, underlying malignancy, infection or autoimmune disease [18].

Hence, due to presence of number of clinical pictures sharing similarities with CRS thereby making the differential diagnosis quite challenging, development of novel diagnostic criteria and tests for CRS have become the issue of high priority in future research.

Cytokines	Effects
IFN- α	<ul style="list-style-type: none"> • Chills, headache, fever, fatigue and dizziness • Activation of macrophages causing excessive release of IL-6, TNF-α and IL-10 [42]
TNF- α	<ul style="list-style-type: none"> • Flu-like symptoms, fever, fatigue, malaria, watery diarrhea, cardiomyopathy, vascular leakage, lung injury. • Stimulate production of acute phase proteins [44] • Vascular leakage, cardiomyopathy • Activation of complement cascade
IL-6	<ul style="list-style-type: none"> • Activation of coagulation cascade causing disseminated intravascular coagulation [45]

IL-6 is considered to play major role in pathophysiology of CRS as it is extremely increased in these patients. Teachey et al. in their study, involving patients with ALL (Acute lymphoblastic leukemia), conducted screening for the biomarkers of CRS following CD-19-CART-cell therapy. They reported extreme levels of IL-6, IL-6 receptors (soluble), sgp 130 and TNF- α in patients developing CRS [46]. Turtle et al. showed highly elevated IL-6 levels in the patients following infusion of CART and in the patients with severe CRS associated with neurotoxicity [47]. Not only cytokines, markers of endothelial dysfunction e.g. von Willebrand factor and Ang-2 are also elevated in CRS thus providing an explanation for occurrence of hypotension, capillary leakage and coagulopathy [38]. A recent post mortem study conducted on the patients who died due to CRS showed endothelium as an important root of elevated IL-6 in CRS [48].

Additionally, cytokines such as IL-18, MIG (Monokine induced by gamma interferon), MCP-1 (Monocyte chemoattractant protein-1) and MIP1 β (Macrophage inflammatory protein 1 β) are also increased in CRS associated with HLH/MAS. The question why not all the patients having CRS develop HLH is still unanswered. However, some of the hypotheses assumed are persistence of genetic variants that could predispose the patients to HLH or deregulation of cytotoxicity of NK (Natural Killer) cells and T-cells induced by IL-6 which might lead to the development of HLH [49].

Biomarkers and Pathophysiology of CRS

The underlying pathophysiology of CRS is rather vast and there is still persistence of lacuna for its complete understanding. Based on features of host, tumor type and therapeutic approach, an inflammatory loop is generated resulting in cytokine storm that has adverse effects to the patients [42].

The cytokines associated with CRS include interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), interleukins (IL) like IL-2, IL-6, IL-8 and IL-10. The cytokines are released following immunotherapy and they further causes the production of more cytokines via stimulation of immune cells [43].

The effects of cytokines secreted are elaborated as follows:

Currently CRP is also being extensively studied as a laboratory marker of CRS and its severity [14]. However CRP is also increased in various infections, so it lacks specificity on demarking infections associated with inflammation from infectious inflammation [50]. It has been observed in previous studies that levels of CRP correlated with the severity of CRS. According to Davila et al. significant differences in the levels of CRP among patients with CRS can be observed within two days after infusion of immunotherapeutic drugs and the level correlated with that of IL-6 [14]. However, since there is still lack of specific biomarkers, studies identifying the same must be encouraged so that CRS can be diagnosed and managed beforehand of its complexities.

Management of CRS

Optimal management of CRS is very challenging as there are still questions left answered regarding safety of anti-cancer immunotherapies. The current scenario of CRS treatment is mainly based on expert opinion from the pioneers in the field of immunotherapy. Currently, treatment approaches followed for CRS focus on two criteria:

- Overcoming the severity of associated symptoms
- Preventing fatal toxicities without hampering antitumor action of drugs administered

Fever is considered an important clinical feature observed following immunotherapy and thus frequent reassessment of CRS signs must be conducted in such patients [38]. All the

patients showing early sign must be regularly assessed to prevent further deterioration. Management of CRS also depends on its grade. Low grade CRS can be treated using antipyretics, anti-histamines and fluids. For high grade CRS various treatment modalities have been developed as follows:

IL-6 blockers

IL-6 is highly elevated in CRS and is also considered a suitable target due to its low importance on T-cell activity. Blockade of IL-6 by tocilizumab has shown significant withdrawal of severe CRS symptoms [51]. Tocilizumab, a IL-6 blocker, is a recombinant monoclonal antibody, that prevents binding of IL-6 with its receptors and hinders both trans and classical signaling pathways. In a clinical trial study patients with severe CRS, administration of tocilizumab showed response rate of 69% [52].

FDA approved tocilizumab in August 2017 for CRS treatment among the patients of age 2 years or more. The dose of drug recommended *via* i.v. applications were 8 mg/kg body weight (for adults) and 12 mg/kg body for weight (for patients with weight<30 kg) till the maximum of 800 mg per dose, which is to be administered at intervals of minimum of 8 hours between the consecutive doses. Patients with CRS of grade 3 or 4 must be immediately supplied with tocilizumab treatment.

Other blockers of IL-6 like situximab and IL-6 trans-signal blocker (sgp130FC) are also available commercially. They also have the potential to blunt CRS but need support from further studies [53].

Corticosteroids

Corticosteroids are the treatment of choice in lowering the effects of CRS in the disorders that involved activated T-cells. Examples of such disorders include inflammatory processes and graft *vs.* host disease [54]. Studies have shown that corticosteroids can be used as a routine supportive care in blinatumomab therapy. According to Porter et al. the patient who received corticosteroids after CART-19 therapy, showed a partial response [21]. It is postulated that steroids (Corticosteroids) when administered *in vitro* reduces the level of cytokines without influencing bispecific T-cell engager associated activation of T-cell [55]. However use of corticosteroids in high dose for long duration can decrease efficacy of CART-cells and limit their anti-leukemic effects [14]. The efficiency of corticosteroids to blunt CRS still needs to be elaborated with further researches.

TNF- α blockers

TNF- α blockers like etanercept and golimumab, infliximab etc. may be effective in some cases of CRS unresponsive to tocilizumab or glucocorticoids. However cases of CRS unresponsive to etanercept have also been published [47].

NOS-inhibitors

As per Xiao et al. NOS-inhibitors such as L-NIL or 1400 W are also shown to relieve systemic toxicities and prevent mortality associated with CRS [56]. This fact has paved ways for the development of new therapeutic modalities that might treat severe CRS effectively. The authors also suggested that NOS-inhibition may contribute to the lowering of requirement of intensive care to severe CRS patients [57].

A3AR agonist (Adenosine A3 receptor agonist)

A3AR against down regulate NF-KB signally pathway (a major pro-inflammatory signaling pathway, inducing the release of number of pro-inflammatory cytokines) and impede the production and secretion of inflammatory cytokines [58]. Highly selective A3AR agonist such as Piclidenoson and Namodenoson exhibited robust anti-cancer and anti-inflammatory activities along with neuroprotective effects and magnificent safely profile upon oral administration in human clinical trial studies. Thus, these agents may be regarded as drug of choice for CRS treatment [59]. A3AR agonist binds to A3AR receptors and hinders the regulation of signal transduction pathways involving NF-KB and Wnt/B-catenin thereby inhibits the production of inflammatory cytokines [60].

Other cytokines which are increased in CRS include IL-ZR, MCP-1 and MIP 1 β . The approaches for management of CRS including use of these inhibitors are in the process of development. They are still to be used clinically while inhibitors of INF- γ , IL-1R and IL-2R have been used clinically [61].

However, it is suggested that further in depth researchers are needed before considering the strategy postulated to be the novel therapeutic modality and also it is recommended to make treatment decisions on the basis of clinical parameters rather than rarely analysing the panels of cytokine released.

Grading Systems of CRS

CRS associated with immunotherapies involving antibodies has been categorized into 5 different grades for the first time by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [12,62,63] as follows:

Grade	Complications	Therapeutics
1	No associated life threatening complications	Symptomatic treatment can be applied
2	Low grade hypotension, mild respiratory symptoms (hypoxia), grade 2 organ toxicity	Moderate therapeutic interventions required For hypotension: -fluids or vasopressors (Low dose) For hypoxia: - low flow oxygen (<48%) → Monitor function of heart and other organs
3	High grade hypotension, hypoxia, grade 3 organ toxicity like coagulopathy, renal dysfunction, cardiac	Aggressive intervention is needed For hypotension: -high dose or multiple vasopressor drugs

dysfunction and grade 4 transaminitis	For hypoxia: -high flow oxygen (<40%) Assessment of cardiac and other organ function Use of immunosuppressants (corticosteroids, tocilizumab)	output, coagulopathy, multiple organ failure, grade 4 organ toxicity, no transaminitis	Use of immune suppressors
4	Life threatening symptoms like potentially low cardiac	Mechanical ventilation	5 Death -

Other grading systems developed are also available as follows [63]:

	Penn grading	Lee et al. [12] grading	MDACC grading
I	Mild reaction Treatment: supportive care (antipyretics and antiemetic)	Mild reaction Treatment: symptomatic e.g. fever fatigue, malaria, headache, nausea	Fever (temperature ≥ 38°C) Organ toxicity (Grade 1)
II	Moderate reaction Organ toxicity (Grade 2 or 3) Treatment: Hospitalization, IV Therapies (excluding fluid resuscitation for hypotensive cases)	Organ toxicity (grade 2) Require moderate intervention Oxygen requirement-<40% Low dose vasopressure Hypotension responsive to fluids	Organ toxicity (grade 2) SBP<90 mmhg Hypotension responsive to fluids or vasopressures in low dose Oxygen need:- FiO ₂ <40% and SaO ₂ >90%)
III	More severe reaction Organ toxicity (grade 3 or 4) Hospitalization required Hypotension require use of fluids and vasopressors in low dose Hypoxia requires oxygenation bi-level positive or continuous positive airway pressure	Aggressive intervention required Oxygen need ≥ 40% Hypotension responsive to high dose or multiple vasopressures Transaminitis (grade 4) Organ toxicity (grade 3)	Organ toxicity (grade 3) Transaminitis (Grade 4) SBP<90 mmhg Hypotension responsive to high dose and multiple vasopressures Oxygen need:- FiO ₂ ≥ 40% and SaO ₂ >90%
IV	Life threatening symptoms Hypotension require high dose of vasopressures Mechanical ventilation for hypoxia	Life threatening symptoms Oxygen toxicity (Grade 4) Mechanical ventilation needed (Transaminitis excluded)	Life threatening symptoms Oxygen toxicity (grade 4) Mechanical ventilation needed (Transaminitis excluded)

MDACC: MD Anderson Cancer Center

Discussion and Conclusion

CRS, the most frequently observed adverse effect of anti-cancer immunotherapies, is considered as the major risk factor for increased morbidity and mortality in patients undergoing immunotherapies. Though valuable insights have been obtained from various controlled and randomized clinical studies about the pathophysiology and management of CRS, there still lie many unanswered questions that have created a lacuna which is to be filled by further studies related to effective management of CRS.

Current basis of CRS treatment strategy involves retrospective analysis, expert opinion and mastery of the physicians in immunotherapy. But there is also necessity of identification of new targets for specific intervention of CRS so that the adverse events subside earlier ensuring the safety and efficacy of therapeutic intervention used.

Since few studies have also shown endothelium to have central role in CRS patho-physiology, further researches providing

valuable insights on involvement of endothelium abnormalities in CRS development are required to as to foster the novel therapeutic modalities. It is also essential to identify the novel biomarkers that could aid in prediction and differential diagnosis of CRS. Further, efficient and easily accessible tools are also to be developed in order to assist clinicians while using therapeutic agents so that adverse outcome of CRS in immunotherapy can be prevented. Also more researches and investigations must be conducted in patients developing CRS such that mechanistic picture related to CRS could be explored in detail there by aiding in development of highly sensitive molecular targets for uprooting the incidence of CRS following immunotherapies.

Though advances made in immunotherapeutic techniques are quite promising, regular use of such treatment modalities requires appropriate recognition and management of potential hazards associated with them. CRS can be presented with mild to life threatening symptoms, therefore it is important for the clinicians to outline the effective management strategy which

not only prevents the life threatening symptoms but also avoids the unnecessary immunosuppression which can lead to the decreased efficacy of immunotherapeutic regimens. More intense studies are needed for better understanding of CRS pathophysiology and as the severity and complications of CRS are dependent on burden of disease, use of such regimens in patients may produce fruitful outcomes with reduced toxicities.

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