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Secondary Immunodeficiency in Hematological Malignancies: Focus on Multiple Myeloma and Chronic Lymphocytic Leukemia

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Secondary immunodeficiency is reported in most patients with hematological malignancies such as chronic lymphocytic leukemia and multiple myeloma. The aim of our review was to evaluate the existing literature data on patients with hematological malignancies, with regard to the effect of immunodeficiency on the outcome, the clinical and therapeutic approach, and on the onset of noninfectious complications, including thrombosis, pleural effusion, and orofacial complications. Immunodeficiency in these patients has an intense impact on their risk of infection, in turn increasing morbidity and mortality even years after treatment completion. However, these patients with increased risk of severe infectious diseases could be treated with adequate vaccination coverage, but the vaccines' administration can be associated with a decreased immune response and an augmented risk of adverse reactions. Probably, immunogenicity of the inactivated is analogous to that of healthy subjects at the moment of vaccination, but it undertakes a gradual weakening over time. However, the dispensation of live attenuated viral vaccines is controversial because of the risk of the activation of vaccine viruses. A particular immunization schedule should be employed according to the clinical and immunological condition of each of these patients to guarantee a constant immune response without any risks to the patients' health.

Keywords: immunodeficiency, infection, multiple myeloma, chronic lymphocytic leukemia, vaccination

INTRODUCTION

General Considerations on Secondary Immunodeficiency: Immunity and Infections

It is possible to classify immunodeficiency syndromes in different manners. A possibility is to separate primary and secondary immunodeficiency. Primary conditions stem from a hereditary alteration of the immune system; this type of disease being usually divided into alterations involving the T-cell system, the B-cells or both B- and T-cells. Generally, they are evident soon in life (1).

Secondary immunodeficiencies (SID) happen more often than the previous ones and generally appears in elder patients as an effect of an external factor, such as human immunodeficiency virus (HIV) infection, malaria, severe liver disease, uremia, malnourishment, splenectomy, diabetes mellitus, cancer and cancer treatment (2). A different cause of SID might be nephrotic syndrome or a protein losing enteropathy with an extreme loss of immunoglobulin. Finally, severe burns may also decrease the immune response.

However, SID generally have a composite pathogenesis correlated to both the principal disease and the effects of its pharmacological treatment (2). Disease-connected SID include solid tumors, chronic and acute lymphoproliferative and myeloproliferative disorders (1).

The clinical effect of SID may extend from a moderately relevant infection vulnerability to a more serious condition distinguished by repeated pulmonary infections, viral or fungal opportunistic infections (1, 3). Moreover, in this type of patient, the diffusion of multidrug-resistant organisms (MDRO), specifically multidrug-resistant gram-negative bacteria, vancomycin-resistant enterococcus and methicillin-resistant staphylococcus aureus augment the incidence of severe infections and mortality. Subjects with disease- or treatment-correlated SID are particularly at risk for lethal infections provoked by MDRO (1). Finally, a frequent reason of impaired immune response is the same infectious condition, which alters the activity of lymphocytes. Finally, the extensive use of cytotoxic treatments and immunosuppressive drugs in tumor subjects can cause a condition of grave SID (4). Therapy-related SID can also happen due to the use of anti-inflammatory and biological medications, especially in transplanted patients (5).

The aim of this review is to evaluate the onset of secondary immunodeficiency in patients with hematological malignancies with a particular focus on multiple myeloma (MM) and chronic lymphatic leukemia (CLL). We will try to evaluate the mechanisms of onset of immunodeficiency, the effectors involved, the effects on survival, the occurrence of complications and possible therapeutic interventions.

CHARACTERISTICS OF SECONDARY IMMUNODEFICIENCY IN PATIENTS WITH MULTIPLE MYELOMA

Epidemiology and Incidence

Multiple myeloma (MM) is a neoplasm of bone marrow plasma cells that provoke intense immunodeficiency (6). Significant progresses in anti-myeloma treatment have enhanced survival (7–11); however, infections cause a fatal outcome in one out of five subjects with MM (12). The risk of getting an infection is highest in the first 90 days after diagnosis, with a third of subjects experiencing severe bacterial diseases that are the cause of about half of early mortality (13, 14).

In MM subjects, the hazard ratios of getting diseases such as septicemia, meningitis, or pneumonia have been shown to be 7.7-, 15.6-, 16.6- and 7.7-fold, respectively, with respect to controls (15). In a study, of the 412 MM subjects studied, 37.4% were reported to develop at least one infectious event, and an incidence of 244 infectious events were recorded. The more frequent sites of infection were the lung and the genitourinary apparatus, while the more frequent infections were bacterial, followed by viral, and *Escherichia coli* resulted in being the most common microorganism. However, in 65.5% of cases, the organism was not identified. Infection was the principal reason of death in 6.3% out of all subjects (16). In MM subjects, risk elements of infection were Durie-Salmon stage IIIB, neutropenia, sex (female), augmented serum creatinine, bad performance status and the presence of a catheter indwelling (17).

Particularly interesting are the data relating to the relationship between MM and hepatitis viruses.

Recently, a study demonstrated an augmented risk of reactivation of HBV after daratumumab administration (18). However, other studies appear to demonstrate a two-way relationship between hematological disease and viral infections. Patients with hepatitis virus infection were reported to have a greater risk of MM, perhaps *via* interference with immunosurveillance (19). In several reports, the frequency of HCV infection in MM has been demonstrated to be greater than in a control population (20), and in a study performed by Duberg and colleagues, there was a relevant argument in the risk of MM onset in subjects with HCV infection for more than 15 years (21). However, a similar correlation was not reported in other studies (22, 23).

A population particularly at risk of infection is that of the MM subjects undergoing transplantation. The degree of hazard of infection in patients undergoing autologous HCT may be distinguished into two phases: pre-engraftment, which is characterized by the occurrence of neutropenia and mucositis, and post-engraftment, which is correlated to a gradual improvement of cell-mediated immunity (24). Before the engraftment, infections essentially involved cellulitis, bacteremia, and gastrointestinal infection (*Clostridium* difficile) (24). The factors favoring the onset of infections prior to starting conditioning treatment comprise kidney insufficiency, smoking, and iron overload. However, the length of neutropenia is the principal risk element after the conditioning regimen is administered (25, 26). The relationship between the iron burden and a greater risk of infectious diseases has been repeatedly described, especially after autologous or allogenic bone marrow transplantation (27, 28).

T-cell normalization happens gradually and is driven by the MM remission condition, the conditioning treatment, the use of radiation treatment, and the type of anti-myeloma treatment (24). Fatal delayed infection after bone marrow transplantation can be provoked by varicella-zoster virus, cytomegalovirus, *C. difficile*, and *Pneumocystis jirovecii*, which provokes pneumonia (29).

Causative Mechanisms of Secondary Immunodeficiency in Patients With Multiple Myeloma

Regarding the mechanisms by which MM patients develop secondary immunodeficiency, all of the effectors of the immune system can be involved in the genesis of SID (**Figure 1**).

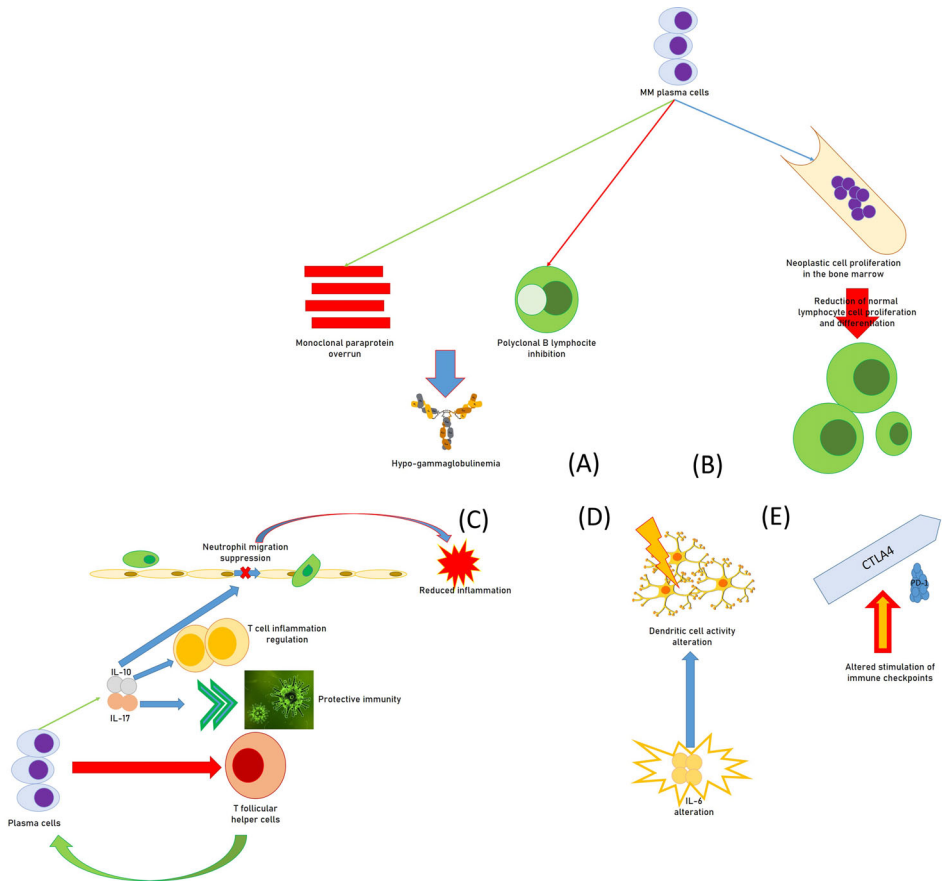

FIGURE 1 | Causal moments of immunodeficiency in patients with multiple myeloma: **(A)** functional hypogammaglobulinemia; **(B)** deficit of the proliferative attitude of lymphocytes; **(C)** regulation of immune functions by plasma cells, with the reduction of T follicular helper cells, the promotion of IL-17, increasing protective immunity against some infections, the source for IL-10, in turn regulating T-cell-related inflammation and suppressing neutrophil-related inflammation; **(D)** alteration of the activity of the dendritic cells by huge immune alterations, including IL-6; **(E)** alteration of the immune checkpoints (altered stimulation of CTLA-4 and PD-1) provoking immunodeficiency.

For instance, an overrun of monoclonal, non-efficient paraprotein and inhibition of polyclonal B lymphocytes by MM plasma cells cause hypogammaglobulinemia, while the proliferation of neoplastic cells in the marrow prevents normal hematopoiesis and determines a reduction in the production of functionally active lymphocyte cells. In fact, in addition to their action in the production of antibodies, plasma cells exert an important role in the regulation of immune functions. For instance, they operate reducing T-follicular helper cells that are essential for the same production of plasma cells in immune reactions that are T-dependent (30). Moreover, CD138hi plasma cells/plasmablasts generate IL-17, a cytokine able to induce protective immunity against *Trypanosoma cruzi* infection (31).

Furthermore, a study suggested that CD138hi cells can be a relevant source of IL-10 which can regulate T-cell–related inflammation (32), while MM cell lines seem able to produce IL-10 (33).

In a report, IL-10 amounts increased with MM progression in patients, and the cytokine quickly suppressed neutrophil migration and reduced neutrophil-related inflammation in an animal experimental model of autoimmune disease (34). It is also important to point out that neutrophils are essential to produce a well-organized immune response against gram-positive bacteria, which are the most common reason for grave infections in subjects with MM and lupus (35).

Moreover, MM patients with a poor long-term survival prognosis had less-replicated cytotoxic T-cell clones, a minor amount of Th17 cells, and a greater number of T-regulatory cells (Tregs) (36). In addition, DC activity might be modified by intense immune alterations of diverse immune components including IL-6, Transforming growth factor-β, and PGE2 within MM bone marrow milieu (37, 38). Altered stimulation of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein-1 (PD-1) immune checkpoints also provoke unwanted immunodeficiency in MM patients (39, 40). B7-H1 is an immunoglobulin-like immunosuppressive molecule largely present in human tumors. It sends an inhibitory signal to its counter-receptor, PD-1, on T cells, thus

provoking T-cell inhibition, MM progress, and chemoresistance (41, 42). In MM patients, the existence of a milieu of immunosuppressive activity has a fundamental role in T-cell immunodeficiency. Several immunosuppression elements are produced by the bone marrow cells, which alter innate and adaptive immune responses (43).

Furthermore, the phenomenon of T-cell exhaustion was reported in many solid cancers and hematological malignancies. This condition is due to a deficiency of proliferative aptitude, reduction of cytotoxicity, an altered delivery of different effector cytokines, such as interleukin 2 and interferon-gamma, and the augmented apoptosis of exhausted T cells (44). An increased presence of T-cell inhibitory receptors is another feature of exhausted T cells (45). For instance, T-cell immunoglobulin and mucin-domain-containing-3 (Tim-3) with its ligand galectin-9 cause CD8+ T-cell alteration and exhaustion in several hematological malignancies (46–48). In recent times, increased inhibitory receptors such as lymphocyte activation gene-3 (LAG-3) on CD4+ and CD8+T cells have been described in peripheral blood from MM subjects before and after autologous transplantation (49).

These aspects have been clarified in a recent study (50), where a relevant increase in both PD-1+CD57+ and Tim-3+CD57+CD3+ T cells and PD- 1+Tim-3+CD3+ T cells was described in blood from MM subjects with respect to controls, and the expression was essentially in the CD8+ T-cell compartment. Moreover, a substantially greater fraction of PD-1+CD3+ T cells was discovered in bone marrow with respect to peripheral blood in MM subjects.

Finally, albeit found in a small number of patients, the finding that after a complete remission, patients exhibited a reduction of the numbers of either PD-1+ or PD-1+Tim-3+ T cells in diverse T-cell compartments in both bone marrow and peripheral blood is extremely interesting (50).

Influence of the Therapeutic Treatment of Multiple Myeloma on the Onset of Secondary Immunodeficiency

Recent reports have proposed that new MM drugs and elevated doses of steroids can determine a permanent risk of infection, even in subjects whose myelomatous disease is well controlled. This infection risk seems to persist high throughout the first year after diagnosis (50). With the use of immunotherapy, therapeutic protocols have an even more pronounced immunosuppressive effect. Moreover, these treatments are maintained for long time, increasing the risk of infection-correlated death.

With regards to SID treatment-related, alterations of innate immunity are crucial (51). Innate immune cells include granulocytes, macrophages, monocytes, and dendritic cells. Numerous groups of pathogen recognition receptors (PRRs), including NOD-like receptors, toll-like receptors, RIG-I-like receptors, and cytosolic sensors for DNA, are recognized to have a relevant effect in host defense (52, 53). Signals from various PRRs determine the passage of NF-κB into the nucleus, leading to a cytokine inflammatory response (54), but MM patients take drugs which block nuclear passage of NF-κB.

When dexamethasone is used, infection provoked by a decline of cell-mediated immunity becomes more probable, which may be realized in the form of mucosal candidiasis or viral or bacterial infections (55, 56). Nevertheless, a 2005 study demonstrated that the overall infection frequency after dexamethasone was comparable to that observed after melphalan plus prednisone (55), even though minor cumulative dosages of dexamethasone considerably reduce the occurrence of grade 3–4 infection, with respect to the usual high dose (57) (**Table 1**).

Thalidomide, a drug with immunomodulatory activity, is not appreciably myelotoxic (28) and exerts both immunomodulatory and immunosuppressive actions on T cells (58, 59). In any case, thalidomide does not seem to augment the risk of infection in MM subjects, as reported in a controlled study of dexamethasone *versus* dexamethasone plus thalidomide (60). This was also reported in a second study that compared melphalan plus prednisone *versus* melphalan plus prednisone with thalidomide (61).

Lenalidomide, a derivative of thalidomide, has more powerful stimulatory actions on CD4+ and CD8+ T cells than thalidomide (62). In a study performed on newly diagnosed MM subjects treated with lenalidomide plus dexamethasone, severe neutropenia (grade III-IV) was infrequent (12%), and only 1 subject presented severe infection (63). In a different report, 68% of subjects on melphalan plus prednisone and lenalidomide presented neutropenia, but only 9% displayed severe infection, a percentage similar to that reported in subjects treated with melphalan plus prednisone (64).

Bortezomib, a proteasome inhibitor, is capable to provoke neutropenia (65); reduction in T cell growth (58, 66); decrease of

TABLE 1 | Influence of the therapeutic treatment of multiple myeloma on the onset of infections.

DRUG	Effect on the risk of infection	Mechanisms	Ref.
Dexamethasone	Increased	Decline of cell-mediated immunity	(55, 56)
Thalidomide	None		(60, 61)
Lenalidomide	None	Neutropenia	(63, 64)
Bortezomib	Increased	Neutropenia Reduction on T cell growth Decrease of NK cells Depression of dendritic cells Change of cytokine production	(25, 58, 59, 65, 66, 68, 69, 71)
Bisphosphonates	Increased	Impairment of neutrophils function	(73)

NK and CD8+ T cells (59); alteration of NK and CD8+T cells function (59); suppression of dendritic cells (67, 68) and changes in cytokine production (69).

Particularly, Bortezomib exerts powerful immunosuppressive consequences on T cells (70, 71). Nevertheless, a controlled clinical study did not report an augmented risk of infection, and the percentages of varicella zoster virus infection were analogous to those of the controls after the introduction of varicella zoster virus prophylaxis (71).

Finally, Bisphosphonates can determine local decrease of immune response with an unidentified system (72), although an impaired neutrophil function may partially contribute to an increased susceptibility to infections (73). Osteomyelitis of the jaw progresses into osteonecrosis (74), *via* diverse mechanisms of both infectious and antiangiogenic types (75, 76). A state of immunodeficiency can favor the onset of septic states capable of inducing osteonecrosis.

The assessment of susceptibility to infections and the risk of infectious complications should be evaluated in each patient before the choice of the therapeutic protocol. This could prevent or limit the onset of an immunodeficiency condition secondary to therapy which could lead to a bad outcome.

Prophylaxis and Therapy of Secondary Immunodeficiency in Patients With Multiple Myeloma

MM patients should be submitted to a risk evaluation preceding the beginning of anti-myeloma therapy on the base of disease- and patient-correlated elements. Multiple myeloma-related aspects able to modify therapy choices include cytogenetic alterations, lactic dehydrogenase concentrations, stage disease, augmented serum Beta2-microglobulin amounts, and others (77). Assessment of host-correlated elements comprises a meticulous anamnesis with specific emphasis on previous infections, a physical evaluation, and a complete evaluation of liver, kidney, pulmonary, and metabolic functions (78).

As for an adequate prophylaxis, the administration of intravenous immunoglobulins (IVIg) for 6–12 months decreased the possibility of severe infections (grade A recommendation, level 1b evidence) (79).

In a recent study, 45 of 295 MM subjects with IgG <5 g/L were defined as SID patients. These patients mostly had repeated infections, particularly pulmonary bacterial infections. The median survival time was considerably shorter in MM subjects with SID (24 *vs* 66 months). More importantly, the multivariate and univariate analysis revealed that IgG <5 g/L was an independent prognostic factor for MM patients (80).

Reduced amounts of specific antibodies against diverse, bacterial, viral, and fungal agents have been reported in patients (81). Nevertheless, not all MM subjects with reduced immunoglobulin levels have infectious problems; moreover, severe infections can occur in the lack of hypogammaglobulinemia. These events could be due to neutropenia or T cell inhibition. B-cell dysfunction augments gradually from monoclonal gammopathy of undetermined significance (MGUS) to Waldenstrom macroglobulinemia to MM (79, 81).

Although the outline of bacterial complications is analogous to that reported in other conditions characterized by neutropenia, most infections in MM subjects are not correlated to reduced neutrophil counts but result from diverse conditions, such as reduced defense capacity of the biological barrier and decreased immune response. In any case, there are only few studies on antimicrobial prophylaxis in MM patients, and for this reason there is some uncertainty for the use of antimicrobial prophylaxis in MM subjects (82).

However, in this setting, preventive treatment with antiviral or antibiotic drugs has been broadly employed (83). Continuous dispensation of antiviral drugs such as acyclovir, famciclovir, or valacyclovir confirmed to be efficient in avoiding herpes zoster virus infections in subjects treated with bortezomib (84). For patients undergoing to autologous transplantation, prophylactic administration of levofloxacin provoked a 27% reduction in infections as well as a 31% reduction in neutropenia or fever (85). Nevertheless, the efficacy of prophylactic antibiotic was reduced by the augmented presence of resistant strains and drug toxicity. Moreover, the administration of antibiotics might provoke unwanted drug interactions and antagonistic effects. In fact, the drugs used in patients with MM, such as bortezomib, corticosteroids, and thalidomide, may be P450 competitors or inducers (86, 87). Therefore, it is important to pay close attention when employing P- 450–related antimicrobial drugs (88).

For these reasons, antibiotics should only be administered for high infection-rate conditions, such as induction treatment, progression, or refractoriness (89). In fact, adding of prophylactic levofloxacin to induction therapy during the first 90 days of treatment drastically decreased febrile occurrences and fatal outcomes with respect to placebo (88).

Finally, there may be supplementary factors motivating the advantages of levofloxacin prophylaxis other than a decrease in infection, and a modification in the microbiome might participate to a decrease in inflammation and an increase in the well-being of these subjects (7).

CHARACTERISTICS OF SECONDARY IMMUNODEFICIENCY IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is a hematological disease with an unpredictable prognosis. This was partially due to the augmented occurrence of infections, and these complications are the main cause of morbidity and death in CLL subjects (90). Generally, infections are of bacterial nature and tended to occur in the lung; however, they can also be located in the gastrointestinal tract, or the skin (91).

Numerous effectors of the immune response are altered in CLL patients, comprising both the alterations of the immune response correlated to the disease itself and the effects of immunosuppression deriving from chemoimmunotherapy of CLL (92, 93).

CLL subjects were described as exhibiting antibody generation reduction (94, 95), and Bussel and Cunningham-Rundles (96) suggested that they might profit from antibody treatment (96).

Reasons for inadequate immunoglobulin concentrations include malfunctioning generation of polyclonal immunoglobulins and anomalous activity of non-neoplastic CD5− B cells; a IgG and IgA class-switch *via* anomalous CD40–CD40 ligand relations and reduction of CD40 ligand; suppression of CD95+ plasma cells in the bone marrow through interaction with CD95 ligand on CD5-B cells; disproportionate inhibition by T-cells; and iatrogenic myelosuppressive treatment (97, 98) (**Figure 2**).

The occurrence of reduced gammaglobulinemia in CLL patients is more marked with advanced-stage disease and linked with patient age and associated pathologies (91). This occurs in CLL subjects with mutated and unmutated immunoglobulin heavy chain genes (99–101).

A 2006 study reported the existence of considerably lower functional antibody amounts against 16 of the 19 serotypes evaluated in old CLL subjects with respect to a group of unvaccinated control subjects (101). As for pneumococcal serotypes, protecting concentrations of antibodies were reported in only 3 of 12 serotypes, in contrast to 9 out of 12 within the control group. This finding suggests that the specific antibody reduction described in CLL patients is correlated to the disease itself and not just a consequence of immune-senescence secondary to aging.

Furthermore, 79% of CLL subjects with a normal IgG amount still had reduced specific antibody reactions to pneumococcus, revealing that IgG evaluation alone is not adequate to recognize CLL subjects who are at increased risk of infection (102). Then, even though British Committee for Standards in Hematology guidelines for the treatment of CLL suggests assessment for total immunoglobulin concentrations as a method of recognizing subjects at risk of infection (103), this approach might be unsuccessful for detecting those subjects with a regular IgG level that have inadequate functional antibody amounts.

Evaluation of IgG antibodies to distinctive antigens results from verified contacts or immunization with specific proteins such as tetanus, diphtheria, or hepatitis B, or polysaccharides such as Salmonella typhi Vi. Specific tests are also available for specific antibodies to herpes simplex virus, Epstein-Barr virus, varicella-zoster virus, and pneumococci. However, in some cases, such as for pneumococcal antibodies, analyses are remarkably inconstant, and evaluation can be troublesome (104).

Complement amounts are also reduced in CLL subjects, especially the C3b fraction, which augments the occurrence of repeated bacterial infections. However, there are also alterations in the stimulation, connection and presence of the complement receptor 1 (CR1) and CR2. Fust et al. reported alterations in the classical complement system in CLL subjects, with a decrease in C1 and C4 amounts in more than 50% of subjects examined (105).

CLL subjects also experience abnormal cellular immunity. Generally, the amount of T helper cells is reduced while the number of T suppressor cells is augmented. Furthermore, CD3+CD8+ T cells generate a decreased quantity of IL-2 and an augmented quantity of interferon and tumor necrosis factor (106–108).

Alterations in phagocyte activity have also been described. Defects in the production of digestive enzymes can involve several types of cells such as neutrophils, monocytes, and lymphocytes. These deficiencies comprise lysozyme, b-glucuronidase, and myeloperoxidase, and the altered production seems to normalize in case of remission of the disease (109).

In CLL, an altered NK cell activity with transcriptional decrease of numerous cytotoxic signaling and decreased stimulating receptor expression has been reported. The NK-cell alteration appears to be of clinical importance, as greater NK-cell amounts is described in subjects with initial disease good

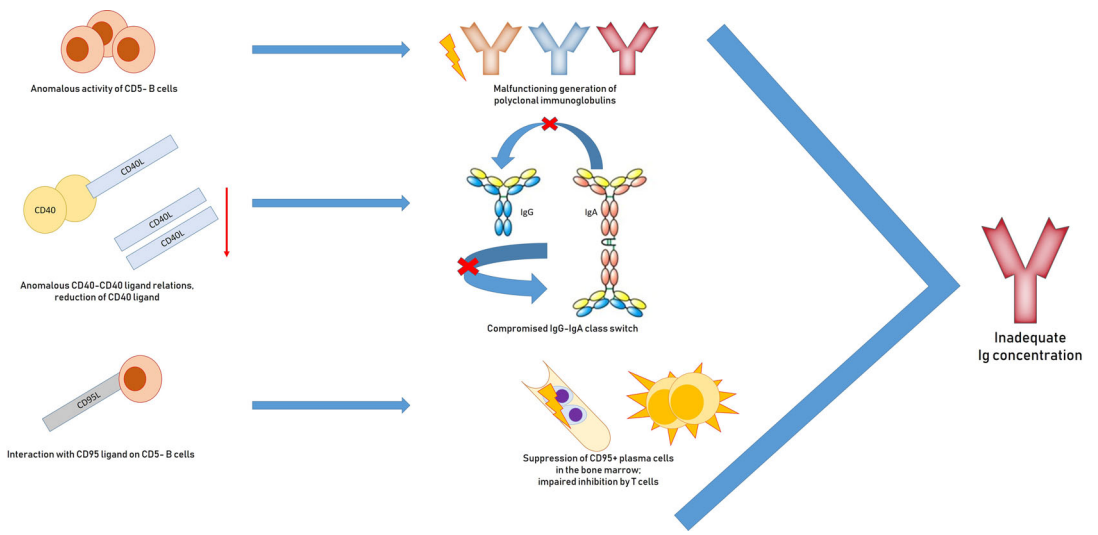

FIGURE 2 | Pathogenesis of hypogammaglobulinemia in patients with chronic lymphocytic leukemia: impaired generation of polyclonal immunoglobulins due to inadequate activation of CD40, suppression of plasma CD95 + cells, impaired inhibition by T cells.

prognosis (mutated IGHV genes), and better NK cytolytic ability is described in subjects with monoclonal B-lymphocytosis (110).

CLL cells generate numerous depressing signals that exert several negative actions on cell-related immunity. For instance, expression of CD200 stimulates differentiation of CD4+ T cells into T regulatory cells, which present CTLA-4, CD270 and PD-L1; these molecules, interacting with their receptors, are able to decrease T-cell growth and stimulation (110).

Gene expression profiling of activated CD4+ cells demonstrated a different modification of T helper function, with a decrease of T-cell receptor signaling and a decrease of cytokine production. This alteration was extremely pronounced in initial CLL but was also demonstrable in other lymphoproliferative diseases, such as follicular lymphoma and extranodal marginal zone lymphoma (111).

Moreover, in CLL, clonal B cells block the activity of normal T lymphocytes *via* the alteration of the establishment of the immunologic synapse in a contact-dependent way (112–114), and being leukemic cells, such depressing cell contacts can be permanent and ubiquitous (115).

A study demonstrated a modification of genes implicated in cell differentiation and cytoskeletal formation in CD4+ T cells, and cytoskeletal formation, vesicle transferring, and cytotoxicity activity in CD8+ T cells. Similar changes in cytoskeletal structure could be produced in healthy allogeneic T cells by co-culturing them with CLL cells. Moreover, modifications in cytoskeletal genes cause a functional alteration in actin polymerization. The result is that T cells from CLL subjects show defective immunologic synapse formation with APCs (107).

Nevertheless, other immunologic alterations are verifiable in these subjects generally due to the same disease or to the treatment (116–122).

Tinhofer et al. reported the existence of CD95 ligand on the cellular membrane of CLL cells, with the molecule being a ligand for the death receptor CD95 (123, 124). Furthermore, an augmented presence of surface CD95 on CLL subjects' CD4+ T cells was demonstrated. These findings suggest that CLL cells could quickly reduce the helper T cell activity *via* this system, which would determine the humoral immunodeficiency in CLL patients (124).

Finally, Sampalo et al. demonstrated the negative action of CLL cells on the plasmatic cell, and the depressing action on the generation of normal immunoglobulin by plasmatic cells was correlated to increased amounts of CLL cells (125).

Prophylaxis and Therapy of Secondary Immunodeficiency in Patients With Chronic Lymphocytic Leukemia. Effects of Chemotherapy on the Onset Of Infections

The simple treatment of CLL does not reestablish a normal immune response and guidelines do not suggest the presence of SID as a motivation for undergoing therapy (126).

Prompt identification of CLL subjects vulnerable to infections and prophylactic dispensation of correct antibiotics is the first approach for the treatment of an antibody insufficiency or SID in patients with CLL (120, 121). In subjects suffering with bronchiectasis, nebulized or low oral dosages of nebulized antibiotics, such as azithromycin, can decrease the occurrence of frequent infections.

The existence of a correlation between the concentrations of a specific class of antibody and the nature of pathogen producing the infection is a debatable issue. However, several authors believe that a reduced production of IgG is often accompanying an infection with streptococcus or haemophilus (107). Instead, IgA reduction is correlated with an augmented occurrence of upper respiratory system infections.

Significant reduction of normal immunoglobulin has been identified to be one of the elements accountable for the augmented vulnerability of CLL subjects to infection; this is the motivation for the use of IG in these subjects (127, 128).

Immunoglobulin replacement therapy (IgRT) may be dispensed intravenously (IV) or subcutaneously (SC). In SID, the effectiveness and safety of SCIG have been reported in numerous subjects with lymphoproliferative diseases and hypogammaglobulinemia (128, 129).

SCIG might present numerous benefits over IVIG as SCIG has been correlated to an enhancement in the quality of life perceived by the patient (130). Moreover, pharmacokinetic characteristics seem greater, as SCIG administration cause higher and more constant IgG concentrations, offering CLL subjects with a more stable defense against infections (131).

In a European consensus declaration, the quantification of serum Ig levels and the concentrations of specific antibodies after vaccination was established as a suitable method for CLL SID subject selection to employ IG (132). However, while in Canada, IVIG and SCIG preparations are commonly employed in SID patients (133, 134), in the EU the accepted indications for IVIG in SID have been expanded from CLL subjects undergoing to allogeneic hematopoietic stem cell transplantation, to subjects who present grave or frequent bacterial infections, unsuccessful antibiotic therapy and serum IgG concentration of <4 g/L (135–138).

Nevertheless, a 14-year retrospective report performed on a big number of CLL subjects established that hypogammaglobulinemia does not seem to modify overall survival (139) and, based on the findings of the first controlled trial on a wide cohort of CLL subjects, IV IgRT was not cost-effective (140). Consequently, the EMA is presently revising its guidelines on the employ of IVIG to evaluate secondary immunoglobulin deficit (141). Their suggested dosage is 0.2–0.4 g/kg every 3 to 4 weeks. However, there is supplemental evidence that SCIG provides efficacious protection in subjects with secondary antibody deficiency (142).

Although IgRT is usually well tolerated in subjects with hematological malignancies, IgRT can on uncommon cases provoke to adverse effects such as hypersensitivity, kidney failure, thromboembolism and hemolysis. Thus, IVIg administration should be carefully examined, especially in subjects with risk factors. Sufficient hydration is crucial. Moreover, when commencing IgRT in subjects with hematological malignancies, the dosage should be weight-based. In obese subjects, IgRT dose should be established on an ideal or adjusted body weight. In any case, SCIg administration might present a lower risk of systemic adverse

events. For this reason, in subjects undergoing therapy for hematological malignancies who are about to begin IgRT, both SCIg and IVIg should be evaluated. Patients should be implicated in the decision on the best route of administration considering their preference. Finally, discontinuation should be considered only after at least 6 months without infections and if there is evidence of immunological recovery. Infection rates should be closely evaluated and IgG levels should be tested during routine patient visits.

Particular attention should be paid to patients with CLL undergoing therapeutic treatment (**Figure 3**).

An adequate prophylaxis is suggested for subjects getting purine- analogue or an anti-CD52 monoclonal antibody, such as alemtuzumab, both during and after therapy. Moreover, a prophylaxis with acyclovir for herpes virus and a *Pneumocystis jirovecii* prophylaxis employing sulfamethoxazole/trimethoprim should be used (Grade of evidence IV, B) (143, 144).

The augmented utilization of new B-cell targeted treatments capable of modifying the function, the differentiation and programmed cell death of B cells, and the use of CD19-targeted chimeric antigen receptor T cells (CAR T) in lymphoproliferative diseases have augmented the occurrence of SID in hematological malignancies (145, 146).

Specific antitumor drugs, as combination chemotherapy, can also increase the risk of some viral infections (91, 101). It has been proposed that these therapeutical protocols synergistically reduce myeloid cells, causing increased immunosuppression and a resulting augmented risk of infection (147, 148). After combination chemotherapy, a higher percentage of grave or uncommon infections have been reported than in subjects treated with fludarabine or cyclophosphamide alone. However, a greater infection-related mortality has not been described by the existing literature. The employment of rituximab, an anti-CD20 monoclonal antibody, in combination treatment with fludarabine and cyclophosphamide (FCR) augments the occurrence of different forms of infections (149). FCR protocols cause deep myelosuppression and a relevant incidence of infections, particularly in older people. Anti-CD20 monoclonal antibodies have been correlated with cytomegalovirus infection or reactivation of hepatitis B and polyomavirus JC infections (150, 151). Recurrence of herpes viruses have also been reported after administration of purine analogs and alemtuzumab (152).

As far the mechanisms underlying the immunosuppressive effects, rituximab provokes a fast reduction of CD20- presenting mature and immature B-cells, which persist at very low concentrations for about 9 months (153). Moreover, rituximab can cause a condition of immunosuppression also *via* the occurrence of a deep neutropenia and a reduction of immunoglobulin levels (154–156). Furthermore, studies also propose that rituximab augments the risk of progressive multifocal leukoencephalopathy (157–159), while an altered humoral immune response with inadequate B-cell growth to simple haptens and recall antigen challenge propose an unfavorable action on memory B-cells (160–162).

Of particular interest is the comparison between the ability of traditional drugs to induce a state of immunosuppression compared to new drugs such as Bruton's kinase inhibitors, phosphatidylinositol 3-kinase inhibitors or B-cl2 inhibitors.

Numerous studies have evaluated the impact of new drugs for the treatment of CLL on the onset of infections. In a multicenter

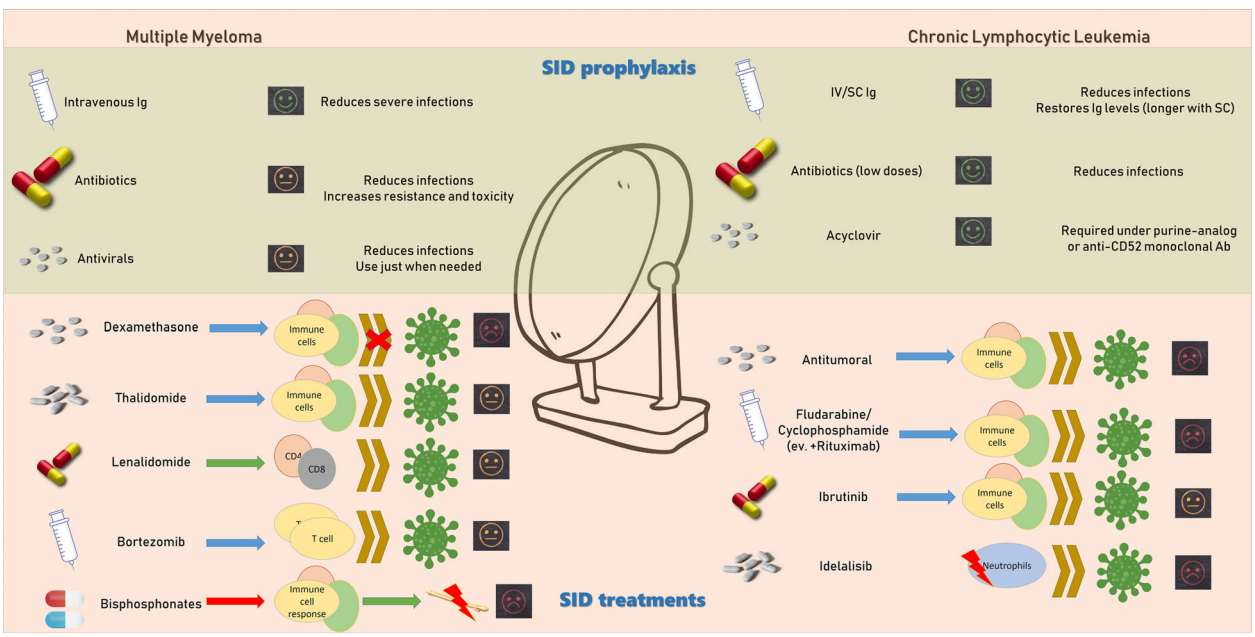

FIGURE 3 | Possible immunological targets of drugs used in the prophylaxis and treatment of secondary immunodeficiency of patients with multiple myeloma and chronic lymphocytic leukemia. Action of antineoplastic drugs on immunological effectors.

clinical trial valuing ibrutinib (a Bruton's tyrosine kinase inhibitor) *versus* an anti-CD20 monoclonal antibody such as ofatumumab in refractory CLL, critical infections of respiratory tract, and urinary tract were analogous in the two groups (24 *versus* 22% of subjects), although CLL subjects on ibrutinib treatment had lengthier treatment exposure (163). The percentage of critical infections was inferior when ibrutinib was administered as first-line therapy (164) (Burger et al., 2015). In the clinical trial with idelalisib (a phosphatidylinositol 3-kinase inhibitor) for refractory CLL, different infections were described such as pneumonia (6%) and febrile neutropenia (5%) (165); a diverse study performed with idelalisib for diverse lymphoproliferative disorders confirmed the occurrence of grave neutropenia (27%) and pneumonia (7%) (166), while a clinical trial on CLL subjects stated 18% occurrence of pneumonia (167). In a phase II clinical trial in refractory CLL, Bcl-2 antagonists, such as venetoclax, have demonstrated an incidence of pneumonia in 6% and febrile neutropenia in 5% of subjects (168).

Regarding the characteristics of immunosuppression induced by new drugs, a study performed on patients submitted to a long-lasting treatment with ibrutinib propose a reduction in the infection occurrence during therapy (169). Two different explanations were suggested. The reduction of the interleukin-correlated T-cell kinase, which can stimulate T-helper cell type 1 CD4 T-cell growth, provoking a decrease of infections, or a restoration of the humoral immunity with an increased production of immunoglobulin A. However, the real reason of an improvement in immunoglobulin function after prolonged treatment remains unidentified (170).

However, it is clear that such new drugs have a lower impact on the immune system of patients with CLL and could guarantee a better safety profile, better adherence to therapy and ultimately a better outcome.

Finally, special consideration was given to the occurrence of neutropenia after therapy with these molecules. The employ of granulocyte-colony stimulating factor (G-CSF) in subjects assuming ibrutinib is infrequent. However, in CLL subjects developing grave neutropenia (ANC < 1.0×109/L), G-CSF has been administered in clinical trials and no side effects were described.

Idelalisib has been correlated to a greater occurrence of grave neutropenia with respect to ibrutinib. The median time to onset of grade ≥ 3 neutropenia was 1.4 months (171), and G-CSF has been administered in 25% of subjects (165).

A phase 1 clinical trial of venetoclax in relapsed/refractory CLL described a 17% of grave infections. The percentage of grade 3/4 neutropenia was 41%, although the percentage of febrile neutropenia was only 6% (172). Analogously in a phase 1b study of venetoclax plus rituximab in relapsed/refractory CLL, the percentage of grave infections was 16% while the percentage of grade 3/4 neutropenia was 53% (173). A phase 2 clinical trial of venetoclax in relapsed/refractory CLL with bad prognosis (del (17p)) described a percentage of grade 3/4 neutropenia of 40%, and febrile neutropenia of 5% (168).

Finally, the number of preceding treatments seem relevant for viral and fungal infections (174).

EFFECTS OF VACCINATION IN PATIENTS WITH SECONDARY IMMUNODEFICIENCY

Safeguarding SID subjects against vaccine-avoidable infections is a frequently ignored field of study (175). However, SID is an obstacle to efficacious vaccination in patients with tumors and chronic infection.

There are essentially two difficulties preventing effective vaccination therapy. The first is the problem that the live vaccine, even if attenuated, could provoke a grave infection. Second, the response to the vaccine in such patients might be inadequate and, subsequently, non-protective (176).

These considerations are particularly valid in patients with hematological malignancies undergoing chemotherapy treatment. An approach with vaccination before the onset of SID would guarantee security and would assure an optimal immune response.

Elements able to condition the effectiveness of vaccination before the onset of SID include the type of hematological malignancy, the vaccine dosage, and the type of chemotherapy treatment given before vaccination.

Prognostic stratification also appears to be a factor capable of influencing the response to vaccination. In a report, after the end of chemotherapy, patients in the low-risk-group demonstrated more often satisfactory antibody concentration against tetanus and diphtheria than patients of the high-risk-group. However, antibodies against tetanus appeared in about 50% of all subjects, and subsequently, re-vaccination antibodies against tetanus were demonstrated in approximately all subjects whereas for diphtheria, this occurred only in some patients. Remarkably, subjects without adequate antibody concentrations displayed a sufficient cellular immune response (177).

Influenza and Pneumococcal vaccination are suggested in early-phase CLL (178), as the vaccination against *Neisseria meningitides*, *Streptococcus pneumonia*, *Haemophilus influenzae*, and other encapsuled pathogen. Vaccination should be performed at least 2 weeks before the beginning of chemotherapy or 3 months after the end of chemotherapy, or 6-12 months after the employ of an anti-B-cell antibody treatment (179). This is mandatory if patients are functionally asplenic or have to be submitted to a splenectomy (180) (Rubin et al., 2013).

Although there are no controlled trials demonstrating that the use of vaccinations may modify infection percentages or prognosis from infectious diseases in CLL, standard vaccinations should be performed in these subjects before the starting of a therapy (179). All live vaccines should be avoided, while conjugate vaccines have proven to be extremely immunogenic and should be suggested in CLL subjects (181).

Lower responses to vaccination in CLL subjects with respect to control subjects have been demonstrated against diverse antigens. Specific antibody generation to polysaccharide antigens, which is expression of a T-cell- independent response, such as classical 23-valent pneumococcal vaccine, is significantly altered in CLL subjects (182). Flawed response to different protein antigens, such as tetanus toxoid is also evident (183, 184).

However, evaluation of vaccine response is difficult and requires special attention. For the analysis of primary responses, an augment

higher than treble after 4 weeks with respect to pre-vaccination concentrations is judged adequate (185, 186).

Hepatitis B vaccine is also suggested for CLL subjects who are devoid of antibodies against HBsAg, and a combination of hepatitis A and B vaccine should be evaluated in endemic areas (187).

However, the bad success of hepatitis B vaccination in the greater part of subjects with indolent lymphomas suggests an altered immune response against this type of infection (188). Failure to response to vaccination may be provoked by a T-cell alteration. A greater rate of ageing CD8+ CD28- T cells presupposes failure to vaccination (189, 190). A decreased naive T-cell set might diminish the amount of T cells presenting a T cell receptor (TCR) that identifies an extraneous antigen, such as HBs. Finally, transcriptional reduction of TCR signaling may also alter T-cell sensitivity to antigenic stimulation.

A reestablishment of a normal immune response could not only allow successful vaccination of CLL subjects but could theoretically enhance prognosis (191, 192).

As far MM subjects, in the CAPiTA clinical trial of 84,496 patients (NCT00744263), a vaccine effectiveness of 45,56% for the 13-valent pneumococcal conjugate vaccine was reported. Vaccination could also help in the prevention of other frequent infections in MM subjects, such as meningitis, influenza, and varicella (193).

Finally, another important obstacle could be due to an altered activity of antigen presenting cells, which are altered in amount and activity (194). In order to bypass this difficulty, the employ of immune adjuvants has been proposed (195).

Despite what has been said about the undoubted opportunity for vaccination of patients with MM and CLL, there are disadvantages and advantages that must be carefully weighed in each patient. Indisputable advantages are prevention of high mortality diseases and complications, the possibility to reduce the use of antibiotics and antimicrobial, resistance development, and finally, the possibility of a herd immunity. However, it must also be considered that inactivated vaccines may be less effective and live-attenuated vaccines have increased risk for adverse reactions. For these reasons, an expert in vaccination should be included for the management of MM and CLL patients to choose the timing, dosage and the need for a possible repeat vaccination in this specific population.

Particular considerations should be done for subjects undergoing autologous bone marrow transplantation (ABMT). In 1995 the Infectious Diseases Working Party of the European Group for Bone Marrow Transplant presented endorsements for re-immunization in subjects who had submitted to allogeneic or ABMT (196) and these recommendations were successively reworked (196), while the Centers for Disease Control and Prevention formulated their proposals (197). Agreeing to these suggestions, a complete vaccination schedule against tetanus, diphtheria, and poliomyelitis is intensely suggested post autologous transplantation for all subjects with hematological malignancies. Moreover, vaccinations against hepatitis B, Haemophilus influenza type B, and influenza are suggested in specific subsets of subjects, while a vaccination therapy aimed at prevention of infections by mumps, pneumococci, rubella, or measles, should be programmed on the characteristics of the individual patient.

A report evaluated if the modifications of immune response described after ABMT would continue in the years after the procedure has been performed. Subjects with lymphoma submitted to ABMT were enrolled. Median time from ABMT was 5 years. Immunophenotyping demonstrated an augment in the amount of B cells, and a reduction in T cells. Moreover, a minor amount of CD4+ T cells caused a diminished CD4/CD8 ratios. The rate of patients presenting CD4+ T cells expressing the 'naive' phenotype CD45RA was 19.5% *vs* 38% in controls. In contrast, the rate of patients expressing the memory phenotype CD45RO was greater in the ABMT group (76% *vs* 54%). After stimulation, greater parts of CD3+CD4+ cells in lymphoma subjects generated IFN-gamma (32% *vs* 16%) or IL-4 (7% *vs* 1%) with respect to healthy subjects. A prevalent Th2 response was described in patients (198).

A different study evaluated the delayed consequences of ABMT on the immune response with regard to vaccines. Vaccination was administered according to EBMT suggestions. The study involved subjects with lymphomas in complete response 4–10 years after ABMT, and a control group. The findings demonstrated that before ABMT the rate of subjects with protective immune response against diphtheria, poliomyelitis, and tetanus was analogous to that of healthy subjects. 4–10 years after ABMT, the percentage of subjects with adequate immune response against diphtheria and poliomyelitis was decreased, while all lymphoma subjects conserved protection against tetanus (199).

In 2017, the U.S. FDA approved the adjuvanted zoster vaccine. Phase 1/2a trials performed on SID patients comprising ABMT receivers and HIV patients, have established that this vaccine is efficacious and secure with no events of varicella zoster infection (200). Currently, the vaccine is suggested in more than 50 years old patients with hematologic malignancies.

Finally, Rapoport et al. accomplished a phase 1/2 trial in patients with a reduced number of lymphocytes after high-dose chemotherapy and ABMT for MM (201). Early post-transplant administration of *in vivo* vaccine primed, and *ex vivo* co-stimulated autologous T cells ensued by post-transplant immunizations reduced the grave SID due to high-dose chemotherapy.

ONSET OF INFECTIOUS AND NON-INFECTIOUS COMPLICATIONS IN HEMATOLOGICAL PATIENTS WITH SECONDARY IMMUNODEFICIENCY

With respect to healthy controls, patients with hematological malignancies undergo several chronic complications correlated to SID, comprising critical, or fatal situations such as endocrine alterations, cardiac and pulmonary diseases, and successive tumors (202). Host risk elements comprise age, and pathological conditions present, while disease-correlated components are motionlessness and the need to control a painful syndrome. Indeed, comorbidities augment with age,

and there is an age-correlated deterioration in functional resources in different systems comprising immune response. Moreover, gerontological alterations, cognitive decline, and community separation all participate to the possibility of complications (203).

Furthermore, there is a bidirectional relationship between non-infectious complications and the onset of infections in patients with hematological malignancies. For instance, the employ of morphine or other pain relievers for bone pain can alter respiratory function, while renal failure is also a risk element for infectious diseases in MM patients, with about 20% of MM subjects displaying an altered renal function. Amyloidosis, and heart failure can arise as consequence of MM, and this is also linked to an augmented risk of infections.

As reported above, infections can cause a state of immunodeficiency, capable of affecting other complications. For instance, B CLL subjects may present a second neoplasm with an occurrence greater with respect to normal subjects (204). In a study, substantial augments were reported for Kaposi sarcoma, lung cancer, melanoma, and laryngeal carcinoma (205). As potential mechanism able to augment the risk of second malignancies in CLL patients, authors propose the immunodeficiency correlated to disease. The effects of SID associated with infections is unclear, but it cannot be excluded or underestimated (205, 206).

The data relating to specific, rare types of cancer appear interesting. Merkel cell carcinoma (MCC) is a neuroendocrine skin tumor with a great tendency for relapse and diffusion. Risk elements for MCC comprise UV exposure, older age, and immunosuppression (207–209). The Merkel cell polyomavirus (MCPyV) is accompanying with MCC in ∼60% to 80% of subjects, proposing an essential effect of the infection and the SID in the onset of this tumor (210). An immunosuppressed condition may stimulate the different phases of MCPyV incorporation, mutagenesis, and carcinogenesis. Indeed, immunosuppressed subjects are over-represented among MCC subjects with respect to normal subjects. CLL has been correlated with augmented risk of MCC (211).

Changes of immune responses may also modify the response to treatments comprising radiation. Local relapse after palliative radiotherapy is greater among MCC immunosuppressed subjects with respect to immunocompetent patients (35% *versus* 9%). Analogous results were found after standard doses of curative-intent radiotherapy on progression free survival among MCC subjects with immunosuppression (212, 213).

Thrombosis is the second most usual cause for death in tumor-affected subjects, and this is due to several factors. In fact, tumor subjects generally present a hypercoagulable state without a clear origin.

Also in this case, there is a bidirectional relationship between non-infectious complications and the onset of infections in patients with hematological malignancies. Although a state of immunodeficiency is generally characterized by a reduced production of NET, as reported above, a dysregulated activation of innate immunity can determine an altered NET production. Recently, NETs were found to cause a hypercoagulable condition, and stimulate the onset of thrombosis (214, 215). Studies performed both in experimental models and in clinical studies have demonstrated that circulating concentrations of NETs are augmented in several forms of tumors (216–218) and may participate to tumor-correlated thrombosis (219). For example, Podaza et al. have reported that neutrophils extracted from CLL subjects presented an augmented ability to discharge NETs, and plasma from CLL subjects is able to instruct neutrophils from normal subjects to produce greater levels of NETs after ex vivo stimulation (218). Likewise, in animal experimental model of chronic myeloid leukemia, neutrophils from leukemic animals were more inclined to produce NETs after stimulation by platelet-activating factor with respect to controls (220). Moreover, NETosis is correlated with lung thrombosis in an experimental model of breast carcinoma, while administration of a low dose of lipopolysaccharide in tumor-bearing animals augments plasma NET biomarkers and causes a prothrombotic condition (220)

Pulmonary emboli usually happen within the first 21 days after transplantation and can be accompanied by fever. Ramsey et al. reported that bacterial infections had occurred in nearly all patients who had had a premortem diagnosis of pulmonary emboli. Opportunistic infections almost always happen within six months, when immunosuppression is highest (221). Pulmonary emboli should be uncommon beyond this time.

A different pathogenetic mechanism is probably the cause of the onset of the hepatic sinusoidal obstruction syndrome (SOS), an obliterative venulitis of the terminal hepatic venules, which is accompanied by an elevated risk of death. SOS, also known as veno-occlusive disease (VOD), happens as an effect of chemotherapy prior to hematopoietic stem cell transplant. An essential pathogenic mechanism is toxic damage of hepatic sinusoidal endothelial cells, with alteration and obstruction of terminal hepatic venules. Causal elements are augmented intrahepatic presence of matrix metalloproteinases and vascular endothelial growth factor, stimulation of clotting factors, sinusoidal endothelial cells glutathione reduction, and nitric oxide diminution. However, a correlation of SOS with SID has been reported (222).

Interesting studies have been conducted on the occurrence of ocular changes in SID patients. Several systemic pathologies as leukemia and anemia, thrombocytopenic purpura, systemic lupus erythematous, diabetes, HIV/AIDS, and hypertension, are recognized to be able to cause retinal lesions (223, 224).

The association of retinal changes with bacterial infections has long been identified (225, 226). Similarly, occurrence of candidal endophthalmitis was also recognized. Two different forms of retinal damage have been reported in the two types of infections: septic emboli, which may cause endogenous or metastatic endophthalmitis, and nonspecific retinal alterations, comprising retinal hemorrhages, cotton wool and Roth spots (227). Moreover, candidal endophthalmitis has been divided into two other types established on the size of the alterations (228). If the infectious event is concentrated within the chorioretinal layers, the name chorioretinitis has been employed. When, in addition to the chorioretinal participation, there is a vitreal abscess, then the expression candidal endophthalmitis is used (229).

Several complications involving the respiratory tract are only in part attributable to infections and in any case find the primum movens in a state of profound immunodeficiency. Opportunistic fungal infections, especially Aspergillus, are a usual reason of morbidity and death in immunocompromised patients and can appear with pneumonia and central airway blockade (230–232). Cases of bronchomediastinal fistula have been described in CLL subjects (233), and bronchomediastinal fistula provoked by endobronchial Aspergilloma may provoke death. Forceful therapy with antifungals and bronchoscopic procedures are mandatory.

Similarly, in studies on pulmonary alterations in immunocompromised patients, the expression interstitial pneumonitis has been employed to designate diverse conditions. Some researchers comprise all parenchymal alterations, while others employ this expression. Finally, other authors employ it for idiopathic pneumonitis, referring to those patients in which no precise diagnosis is present. Interstitial pneumonitis in the subjects with hematologic malignancies who experienced bone marrow transplantation has a diverse meaning. It can be due to cytomegalovirus infection or may be idiopathic. However, infrequently, it may be due to *Pneumocystis carinii*, herpes simplex, and it is correlated to a high mortality (more than 50%) when the subject presents severe graft-versus-host disease (233, 234). Introduction into clinical practice of prophylactic employ of trimethoprim sulfamethoxazole in these subjects reduced the onset of *P. carinii* infections (235).

Clinical symptoms of interstitial pneumonitis after allogenic BMT are characterized by the presence of fever, rattles, tachypnea, gasp, reduced Pa02, and radiologic evidence of an interstitial process. Generally, interstitial pneumonitis starts two months after transplantation and happens in 20 to 30% of recipients. The development of interstitial pneumonitis was an independent variable shown to significantly impact on TRM and OS (236).

Aspiration pneumonia, which generally happens in the debilitated subjects, may dispose the SID patient to secondary bacterial infections, comprising anaerobic infections and their complications. The adult respiratory distress syndrome, happens acutely and simulates other acute complications.

Rather frequent causes of pleural effusion in the SID patients are bacterial pneumonia, comprising that provoked by *Legionella*, while unusual causes are *Nocardia*, and rare are *Pneumocystis, C*ytomegalovirus, Herpes virus, and invasive fungal disease (235).

Orofacial Manifestation

Orofacial expressions of hematological malignancies and SID are frequent in leukemic patients (237) (Adeyemo et al., 2011). Gingival enlargement with limited or complete cover-up of the crowns of the teeth is a usual finding, especially in acute monocytic leukemia, and it is due to the total permeation of the gingiva by clonal cells. The augmented predisposition to oral bleeding prejudices an adequate oral hygiene and provokes gathering of microbial plaque which operates as an inflammatory incentive for an overstated reaction to plaque with consequent formation of connective tissue hyperplasia of the gingival and augmented periodontal damage (238–241).

Neutropenic mucosal ulcerations are reported in nearly half of leukemic subjects and this complication happens when the number of neutrophils falls below 1000 neutrophils/mm (242). Augmented vulnerability to infections and appearance of pericoronitis, or periapical and periodontal aching inflammations are common in SID patients (243–245) as necrotizing ulcerative gingivitis, and hairy leukoplakia (246). Palatal necrosis and necrotic lesions of the palate may be found in subjects with acute leukemia (247).

In leukemic patients, the immunosuppressive actions determined by the treatment, especially steroid therapy, can provoke the onset of oral mucositis, which can happen without a viral participation, as thinning of the mucosa and the presence of bone marrow inhibition which permit the onset of other opportunistic infections able to damage mucosa. This may be avoided by scrupulous buccal cleanliness and administration of topical antimicrobial drugs (248).

MM subjects have a deep immunosuppression; thus, several forms of buccal alterations may be recognized in this type of patients. These comprise oral hairy leukoplakia (249, 250), while amyloid accumulation in the tongue can also provoke the onset of macroglossia with atrophic tongue or translucent papules on the buccal mucosa or the tongue (251).

SID AND CANCER RISK

As highlighted, the relationships between neoplasms and infections are bidirectional. While it is true that tumors inducing immunosuppression are capable of causing the appearance of infections, it is also true that many infections have an oncogenic capacity. Chronic infection is one of the main reasons of tumor, and there are numerous pathogenetic moments to explain infection-correlated oncogenesis, and microorganisms can provoke the onset of tumors through the determination of important and chronic inflammatory states, the implementation of an intrinsic oncogenic potential, and above all the onset of a severe immunodeficiency capable of conditioning escape from host immunity (252).

SID subjects are at augmented risk of acquiring lymphoproliferative neoplasms, as indeed found in patients with primary immunodeficiency (253).

In MM patients, microorganisms presenting pathogen-associated molecular patterns can stimulate toll-like receptors on MM cells, hasten MM cell proliferation and inhibit chemotherapy-provoked programmed cell death (254–256). Furthermore, by stimulating the delivery of immune mediators, infections can speed up tumor advancement (257, 258). For this, by rapidly eliminating the pathogens and changing the pro-inflammatory immune microenvironment, drugs with anti-infective activity can have both anti-tumor and anti-infection capacities.

Based on what has been said, it is evident that a careful evaluation of the state of immunocompetence is necessary in all patients with hematological malignancies. To assess the effect of immunological changes and to control subject suffering from hematological malignancies, a careful clinical history of infections, an evaluation of serum immunoglobulins (259) and a quantification of lymphocyte subsets, comprising both CD4,

CD8 T cells and B cells are suggested at the diagnosis and after chemotherapy. Neutrophil assessment should be also frequently controlled (260).

A study has underlined the extreme relevance of regular routine immunological appraisal for secondary specific antibody insufficiency to protein immunization in CLL patients as an approach for identifying the most susceptible subjects to infections. These analyses should be performed every 6–12 months and always after the appearance of relevant infections, and after a chemotherapy (91).

FUTURE PERSPECTIVES

A promising field of study appears to be that of drug repositioning, with the possibility that drugs employed for the therapy of infectious diseases may be advantageous in the treatment of hematological neoplasms, especially in immunosuppressed patients (261). It was established *in vitro* that the anti-infective chloramphenicol could stimulate MM cell death in a dose- and time-dependent way (262). Contemporarily affecting two essential intracellular protein degradation mechanisms of the ubiquitin-proteasome and the autophagylysosome system, chloramphenicol causes endoplasmic reticulum stress related apoptosis and the production of the pro-apoptotic transcription factor CADD153 able to induce programmed cell death in MM cell lines (263). Further, thalidomide and clarithromycin were reported to synergistically decrease IL-6 and TNF-α production possibly through ERK1/2 and AKT block (264).

A different area of study could be constituted by the serial evaluation over time of the immunological alterations that characterize conditions such as MGUS and MBL. It is in fact known that patients with MBL, a precursor to CLL, show defective synapse formation between B cells and T cells which worsens with MBL's progression to CLL. A careful study of these patients could uncover the immunological mechanisms that favor the progression of these conditions towards an overt disease and could suggest new approaches to prophylaxis and therapy for both hematological neoplasms and infectious complications.

Finally, a different issue that should certainly be studied is that of vaccination of patients with hemopathies due to the difficulties it manifests and the possibilities it offers, and the implications inherent in vaccination practice in patients with hematological diseases emerge strongly in the current pandemic period. Patients with hematological malignancies have an augmented risk for critical COVID-19 disease and mortality. Herishanu et al. evaluated immune response to the BNT162b2 messenger RNA COVID-19 vaccine in CLL subjects. A comparison between patients and healthy controls demonstrated a significantly diminished response rate among patients. The response was greater in CLL subjects who attained clinical remission, followed by treatment-naive patients and only 16.0% in subjects under treatment at the time of vaccination. In CLL subjects treated with Bruton's tyrosine kinase inhibitors or venetoclax ± anti-CD20 antibody, response rates were significantly low. None of the CLL subjects treated with anti-CD20 antibodies <12 months before vaccination responded (265). All this confirms the difficulty of vaccination in patients with hematological malignancies.

A possible useful approach could be to vaccinate subjects at Monoclonal Gammopathy of Undetermined Significance and Monoclonal B Lymphocytosis stages (for MM and CLL, respectively) or at initial phase of B-cell malignancy diagnosis, when a better antibody response could be obtained with respect to more advanced stages (260).

Moreover, many of the difficulties encountered in vaccinating SID subjects are like those encountered in implementing an adequate vaccination against tumors. Nevertheless, vaccinotherapy aimed at the treatment of tumors has great prospects in treating hematological malignancies and may offer a complementary treatment modality to treat these diseases with respect to traditional chemotherapy. New approaches comprise genetic manipulation of autologous T cells with receptors for tumor-specific epitopes, administration of vaccine-primed and *ex vivo* costimulated autologous T cells after high dosages of immunosuppressive drugs such as melphalan, infusion of dendritic cell/plasma cell fusions and employ of expanded marrow-infiltrating lymphocytes. The mission in the future is to assess these strategies in apposite clinical groups of patients, and to combine them with schemes to overwhelm immunoparesis as a method to generate a strong immune response (266, 267).

CONCLUSIONS

In conclusion, the mechanisms underlying the appearance of SID in patients with hematological malignancies are different and are correlated to the neoplasms and the same treatments. The multiplication in therapeutic opportunities for these diseases makes it of utmost importance to gain a better understanding of the effects of new therapies on the various components of the immune system and the prevention of infectious complications. Immunotherapies are revolutionizing the treatment of hematological malignancies. Moreover, by suppressing the pro-inflammatory microenvironment and pathogens, prophylactic and therapeutic antibiotics represent anti-tumor and anti-infection properties. Combined therapies integrated with optimized modern clinical management will continue to deliver better anticipations for patients in years to come. Hopefully, the collaborative efforts from hematologists, infectious disease specialists, pathologists, pharmacologists will ensure the best management of these patients.

AUTHOR CONTRIBUTIONS

Conceptualization, SG and AA. Methodology, CM AT and GP. Software, AT. Formal analysis, AT, CM, GP. Data curation, GP and AT. Writing—original draft preparation, AA. Writing—review and editing, AA and SG. Supervision, AA and SG. All authors have read and agreed to the published version of the manuscript.

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