Progress in treatment of viral infections in children with acute lymphoblastic leukemia

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Abstract

In children, the most commonly encountered type of leukemia is acute lymphoblastic leukemia (ALL). An important source of morbidity and mortality in ALL are viral infections. Even though allogeneic transplantations, which are often applied also in ALL, carry a recognized risk for viral infections, there are multiple factors that make ALL patients susceptible to viral infections. The presence of those factors has an influence in the type and severity of infections. Currently available treatment options do not guarantee a positive outcome for every case of viral infection in ALL, without significant side effects. Side effects can have very serious consequences for the ALL patients, which include nephrotoxicity. For this reason a number of strategies for personalized intervention have been already clinically tested, and experimental approaches are being developed. Adoptive immunotherapy, which entails administration of *ex vivo* grown immune cells to a patient, is a promising approach in general, and for transplant recipients in particular. The *ex vivo* grown cells are aimed to strengthen the immune response to the virus that has been identified in the patients' blood and tissue samples. Even though many patients with weakened immune system can benefit from progress in novel approaches, a viral infection still poses a very significant risk for many patients. Therefore, preventive measures and supportive care are very important for ALL patients.

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Introduction

According to the National Comprehensive Cancer Network (NCCN) guidelines, which are a most valuable resource for cancer, acute leukemia is considered a disease condition with high risk for infectious complications. In children, the most commonly encountered type of leukemia is acute lymphoblastic leukemia (ALL).[1] ALL, in particular, is the most prevalent type of neoplasia in pediatric cancer patients undergoing chemotherapy, which develop acute respiratory viral infections.[2] Even though allogeneic transplantations, which are often applied also in ALL, carry a recognized risk for viral infections, there are multiple factors that make ALL patients susceptible to viral infections.[3] The presence of those factors has an influence in the type and severity of infections.

The development of ALL as a disease itself has been attributed to a lack of mobilization of the immune system, due to decreased exposure to infectious agents.[4] A weak immune surveillance would permit onset of ALL, and in parallel be accompanied by a weak defense against viral infections. Both susceptibilities (to ALL and viruses) can be attributed to an impaired ability to induce increases in stimulants of the adaptive immune response such as interferon gamma (IFNγ) and interleukin-12 (IL-12), and conversely increased capacity to secrete immunosuppressive hormones such as transforming growth factor-β and IL-10.[5-7] Feedback regulation of transcription factors that control cytokine gene expression is not intact in malignant disease.[8,9] In fact, ALL is associated with evidence for a cytokine imbalance at diagnosis, for example decreased steady state levels in IFNγ and increased levels of IL-10.[5,10,11]

Disease progression of ALL further impairs function of the immune system, as ALL is by definition an immunosuppressive disease that has been notably linked to neutropenia.[12] Additionally, most effective therapeutic strategies for ALL are immunosuppressive.[13] This includes steroids, which have been linked to *Varicella-Zoster* virus (VZV) infections.[14] Loss of humoral immunity in ALL is considered particularly serious.[15] After therapy, B- and T-lymphocytes need between six months and one year to recover the full range of their activity. Furthermore, therapeutically applied virus as part of the antileukemic scheme has been reported as causative of a fatal infection, where a live attenuated VZV vaccine was used as part of the therapeutic strategy.[16]

Also factors that concern individual patients, such as genetic alleles that encode specific antigens can affect susceptibility to virus infection. For example the *DEFB1* gene haplotype [encodes β-defensin-1 (hBD-1)] was associated with herpes viruses prevalence in the serum of children with acute lymphoblastic leukemia.[17] In particular, carriers of the GCA haplotype were found to have a significantly higher rate of antibodies against cytomegalovirus (CMV) and *Herpes simplex* virus (HSV) in ALL children compared to controls (CMV: 68 *vs* 29%, P=0.006; HSV: 56 *vs* 26%, P=0.04, respectively), while no association was found for antibodies against Epstein-Barr virus (EBV) by GCA haplotype in

case and controls (58 *vs* 40%, P=not significant).[17] This suggests that leukemic patients carrying untranslated variants of hBD-1 have a higher susceptibility to herpes virus infections than controls.[17]

Finally, in cases that need allogeneic transplantation, T-cells are pharmaceutically depleted to prevent graft-versus-host disease (GvHD).[18] This depletion of lymphocytes removes an important barrier against viral infections.[19] As an association of human leucocyte antigen class II polymorphic variant with incidence of precursor B-cell and T-cell ALL was made, it would be interesting to learn if this has effects on the susceptibility to viral infections.[20]

ALL patients may suffer from viral infections through reactivation of a latent, preexisting virus due to the patients' weakened immune system (for example CMV), especially after the additional immunosuppressive regimen for allogeneic transplantations, or by infections that occurred after onset of ALL, which include nosocomial infections.[21,22] In viral infections where symptoms overlap, microbiological diagnosis and contact preventive measures are crucial, and strict isolation for all patients admitted on hospital ward during seasonal outbreaks of viruses that pose a severe risk to immunosuppressed patients is recommended.[23,24]

All patients who meet the criteria for examination should be tested for a precipitating infection, including culture of blood and urine, depending on symptoms chest radiography, and screening for EBV, CMV, parvovirus B19, human immunodeficiency virus (HIV), and human herpes virus-6 (HHV6).[25] The nasopharyngeal aspirate can also give information on the presence of virus in acute respiratory infections of pediatric ALL patients.[2] An example of sensitive method for diagnosis of active viral infection, and also a reliable marker of successful clearance of virus from the blood is real-time polymerase chain reaction (PCR), as it is used to monitor for CMV.[26] At least in the case of CMV it is considered a more reliable marker than antigen detection.[26]

Our search strategy included use of the data available in Pubmed, Centers for Disease Control and Prevention (CDC; www.cdc.gov), the registry of patient studies ClinicalTrials.gov, and NCCN (www.nccn.org) for the terms that describe all viruses described herein, their pathology, and intervention methods that include clinical, translational, and experimental approaches.

Consequences of viral infection or reactivation

Types of viral infections that occur during ALL, especially after allogeneic transplantation, can have serious consequences, include adenovirus (ADV), EBV, CMV, VZV, BK, HHV6, HSV, and influenza virus.[18,27-29] Even though in healthy children most of these infections can be overcome without serious consequences, in ALL patients they can cause serious morbidity and can even lead to a fatal outcome.

Many of the characterized virus types that are associated with fatal outcome (VZV, CMV, HHV6, EBV, HSV), belong to the herpes virus family, Herpesviridae. In particular, these herpes virus family members (VZV, CMV, HHV6, EBV, HSV), are known to cause serious complications, and in some cases death of ALL patients. Most of these viruses can be identified by large-scale multiplex PCR.[27] It is very interesting that at least two viruses that belong to this family have established the capacity to interfere with the function of the immune system by producing homologues of immune modulators of the host, notably the cytokine IL-10. CMV and EBV generate polypeptides (cmvIL-10 and ebvIL-10, correspondingly) that modulate the immune response against virus and, experimentally even against the malignant cells.[30] Specifically, viral IL-10 was shown experimentally to activate transcription factor STAT3 and repress the cytokine tumor necrosis factor-α in mammalian cell lines.[31,32]

Cytomegalovirus

CMV is a well-known risk for transplant recipients (*e.g.*, resulting in pneumonitis, or ventriculoencephalitis), which is monitored by PCR.[33-35] Patient CMV seropositivity with or without reactivation is the most important prognostic factor for survival and treatment-related mortality in stem cell transplantation from unrelated donors using pretransplant *in vivo* T-cell depletion with anti-thymocyte globulin. By multivariate analyses, CMV seropositivity remained the strongest independent negative factor for treatment-related mortality (relative risk: 5.3; confidence interval: 1.9-14.6; P=0.002).[36]

Pathology of viral infections in ALL can be exacerbated by adrenal insufficiency. Adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal axis by the glucocorticoid (GC) treatment in ALL may aggravate the effects of infections.[37] Particularly after hematopoietic stem cell transplantation (HSCT), adrenal insufficiency may follow the GC administration that is used to ameliorate GvHD.[38] Although rare, CMV infection itself has also been reported as a primary cause of adrenal insufficiency, necessitating early diagnosis and treatment.[39,40]

Adenovirus

ADV infection of ALL patients during standard chemotherapy can lead to hepatitis, which can be fatal.[41,42] On the other hand, systemic ADV infection has been noted after death from multiple organ failure, in an ALL patient that had undergone allogeneic peripheral blood stem cell transplantation.[43] In general ADV infection is a frequent complication after stem cell transplantation from alternate donors in the pediatric population.[44] This makes it necessary to develop innovative treatment modalities that can improve the prognosis of ADV-infected, immunecompromised patients.[45]

Varicella-Zoster virus

VZV infection has been also reported in connection with a high-dose glucocorticoid dexamethasone administration.[46,47] VZV can be fatal both by infection of the ALL patient, as well as after reactivation of a latent VZV infection in the immunocompromised patient.[47] Liver failure due to VZV infection has been early recognized as a fatal complication in ALL.[48]

Herpes simplex virus

There have been reported deaths of transplant recipients from HSV pneumonia in spite of the use of acyclovir and foscarnet, and in spite of *in vitro*-sensitivity of HSV isolates from those pediatric ALL patients to foscarnet.[49] HSV was also documented by immunohistochemistry and PCR, after autopsy of a 22-year old patient that died from multisystem organ failure, while in remission after chemotherapy for ALL.[50]

Epstein-Barr virus

EBV, which can cause lethal infections also in ALL remission, may cause hemophagocytic lymphohistiocytosis (HLH), a syndrome of impaired immunity that presents an uncontrolled hyperinflammatory response.[25,51] EBV-linked fatal hemophagocytic syndrome can result to bone marrow and hepatic failure.[52]

Comparison of IFNγ, IL-10 and IL-6 may be useful for distinguishing between bacterial sepsis, viral infections, and HLH. Using the criteria IFNγ >75 pg/mL, and IL-10 >60 pg/mL, sensitivity and specificity of diagnosing HLH is 98.9 and 93.0%, respectively.[53] Apart from EBV, CMV, HHV6, parvovirus B19, and HIV can cause HLH, however EBV is the most consistently reported virus associated with HLH.[25] EBV reactivation can complicate presentation of other infections including CMV and HHV6.[54]

Human herpes virus-6

HHV6 is increasingly recognized as an important opportunistic pathogen.[55]

HHV6 can complicate the clinical presentation of other infections including CMV, and is likely also inherited through the germline.[56]

Human immunodeficiency virus

HIV infection in patients with hematological malignancies, determined by the presence of anti-HIV antibodies has been reported. It was mostly encountered in patients diagnosed with B-cell lineage derived malignancies.[57] Perinatally transmitted HIV has also been reported in the case of a five-year old child with pre-B cell ALL. The child was successfully treated with anti-retroviral agents.[58] Currently a clinical trial is recruiting HIV-positive hematologic cancer patients (NCT00968630).

Rhinovirus

In children, in general, rhinovirus infection has shown the potential for a more severe clinical course than respiratory syncytial virus (RSV) and influenza A/B infections.[59] There is no widely used rhinovirus-targeted treatment, however several agents including pleconaril, BTA-798, and inhaled IFN-β 1a (SNG001), are being tested in the general patient population with rhinovirus infections.[60] Globulin-replacement therapy is generally not helpful, because the infectious burden of rhinovirus in HSCT recipients is mainly due to impairment of the T-cell mediated immunity.[61]

Respiratory syncytial virus

The presence of RSV is not rare in nasopharyngeal aspirate and blood samples of patients with neoplasia and acute respiratory infections.[2] For RSV, which is monitored by real-time PCR, next to the NCCN-recommended ribavirin, at least one possible option, both for prophylaxis and also for persistent or serious RSV infection of pediatric ALL patients, is Palivizumab, a humanized monoclonal antibody directed against the fusion protein of RSV.[62,63] Resistance to palivizumab is relatively rare but possible.[64] Experimental treatments that include a small interfering RNA are under development.[65,66] It is important to note that RSV is reportedly very common in pediatric autopsies of patients with severe respiratory infectious diseases, and may be the most common virus identified after deaths that have not been linked to a pandemic.[67,68]

Parvovirus B19

Parvovirus B19 can kill a patient in the event that the resulting pneumonia does not respond to treatment.[69,70] Apart from pneumonia, the development of a B19-associated HLH is also possible.[71]

Influenza virus

Influenza virus, in particular the H1N1 type, is well known to become lethal in patients that have compounding serious health problems.[28]

Norovirus

Norovirus (NV) can also be fatal in immunocompromised patients, and this could pose a risk to ALL patients, especially after HSCT.[72] Norovirus causes gastroenteritis, where elevated blood lactate was proposed to assist in predicting mortality.[73] While ribavirin, interferons, and immunoglobulins might have some benefit to the patients, an effective vaccine is urgently needed for this virus.[73-75]

Other viruses

Also reactivation of *polyomaviruses BK* and *John Cunningham* virus is increasingly prevalent cause of morbidity and mortality in immunocompromised patients.[76] Primary infection occurs during childhood through respiratory or urino-oral transmission.[77]

Other viruses that posed a lethal threat to ALL patients in the past such as the measles virus, are far less frequently encountered today; among several reasons, due to progress in vaccine development, and years of implementation of population-wide vaccination programs (measles-mumps-rubella vaccine).[15,78-80]

Limits of established methods for treatment of viral infection and prophylaxis against viral reactivation in acute lymphoblastic leukemia patients

As there is currently no drug that can be guaranteed to cure severe viral infections in patients with compromised immune system, the optimum choice of treatment is subject of ongoing discussion and improvements. Two main sources of published guidelines can be mentioned here, namely the non-profit NCCN and the public health institute CDC, a federal agency under the Department of Health and Human Services (one brief summary of recommended antivirals is provided in Table 1).

Neutropenia

For neutropenia, which is a contributing factor for infections during chemotherapy, myeloid growth factors are recommended as primary prophylaxis; in consideration of the burden of cost for healthcare for febrile neutropenia and the prophylaxis, it is recommended to focus on therapeutic benefit.[81,82] In regard to treatment aimed at the virus, an important fact is that often the antiviral agents used against a virus that proved resistant to the first line drug, often carry a significant burden of potential side effects.

Cidofovir and its alternatives

The choice, therefore, needs to take into account the ability of the patient's organism to tolerate specific toxic agents. For example, the agent cidofovir has been gradually changing position in the NCCN top choice list of agents used for CMV prophylaxis during the last two years, mainly due to substantial nephrotoxicity. Currently the NCCN panel recommends valacyclovir or acyclovir as prophylaxis against CMV reactivation, and monitoring by PCR or antibody-based methods.[22,83,84] In 2015 cidofovir is regarded as a third-line treatment option for CMV, while foscarnet is generally a more preferred option for acyclovir-resistant CMV (foscarnet could be applicable even in neonates) due to less (but still significant) potential nephrotoxicity.[85] Monitoring of drug resistance to ganciclovir, foscarnet and cidofovir is performed by genotyping.[86-89]

Hyperimmune anti-CMV globulins have been also used as a passive form of immunization, for prophylaxis against CMV with some success.[35,90] Acyclovir, valacyclovir, and famciclovir are recommended for prophylaxis against HSV reactivation, especially for transplant recipients (both autologous and allogeneic) and for a long time period, of over 30 days, recipients of allogeneic HSCT, in case of GvHD or of frequent HSV reactivations before transplantation. However, patients who already receive foscarnet or ganciclovir to prevent CMV reactivation do not need additional administration of acyclovir.

ADV, and several other viruses are also treated with cidofovir, which in those cases might be better tolerated than in CMV infections.[91] Alternatively, treatment with a modified dosing regimen of cidofovir was well tolerated and high-risk ADV infections resolved in seven pediatric allogeneic hematopoietic progenitor cell transplant recipients.[92]

For HSCT patients that were seropositive for VZV before the transplantation, the NCCN panel recommends prophylaxis with acyclovir for at least 1 year after HSCT. This prophylaxis should be extended in cases that immunosuppressive treatment is prolonged. Drugs used in prophylaxis against HSV are active also against VZV. In contrast, valacyclovir and acyclovir have only weak activity against CMV, even though they

have a good safety profile.[22] Therefore, surveillance and preemptive therapy with ganciclovir or foscarnet is still required for patients that are seropositive for CMV. Another, less studied but potentially fatal herpes family member, which may prove sensitive to ganciclovir, foscarnet or cidofovir is HHV7; can be detected by nested PCR and antibody-based methods, including the enzyme-linked immunosorbent assay (ELISA).[93-95] It may cause mutually exclusive infections with HHV6, and can lead to lethal encephalitis.

In the case of influenza virus, established prevention and treatment methods have a good record also for ALL patients. Neuraminidase inhibitors, for instance, improve outcome of patients with leukemia and influenza; however, the best protection from pneumonia is offered by preventive vaccination.[96-98]

Another virus that can become reactivated during immunosuppression is hepatitis B virus (HBV), for which lamivudine was recommended for prophylaxis, with the additional note for a need for extended use in cases of prolonged immunosuppression of patients that are positive for the HBV antigen; however resistance has been often noted, and therefore it is recommended to use in combination with other drugs such as adefovir.[99,100] A far lower probability of resistance, exists for tenofovir and entecavir and therefore either one of these two drugs can be considered as an effective monotherapy.[101,102] Conversely, tenofovir and entecavir are not recommended to use in combination, unless a very high viral load is present (NCCN prevention and treatment of cancer-related infections, version I, 2015). Detection of HBV can be made by detection of antibody to hepatitis B core antigen, and by PCR-based determination of serum HBV DNA level.[103,104]

Several drugs have been removed from the list of preferred agents against virus-resistant disease, due to the lack of evidence for a curative substantial effect. In contrast, toxic drugs such as *e.g.*, cidofovir remain as important treatment options, especially for CMV, due to numerous evidence-based studies that have demonstrated high antiviral activity.[105,106] A lipid conjugate of cidofovir labeled CMX001 (brincidofovir) is increasingly used against DNA viruses (ADV, CMV, polyoma, *etc.*).[107,108] CMX001, is an orally bioavailable derivative of cidofovir (hexadecyloxypropyl cidofovir), and recently completed a phase II clinical trial for preemptive treatment of ADV (NCT 01241344).[109]

Advancing frontier of treatment

Currently available treatment options do not guarantee a positive outcome for every case of viral infection in ALL, without significant side effects. For this reason a number of strategies for personalized intervention have been already clinically tested, and experimental approaches are being developed to translate progress from basic and preclinical research into specific treatment strategies (www.clinicaltrials.gov). Personalized intervention can be effective, however, to date high cost prevents a wider application. Experimental approaches on the other hand, may limit cost of treatment and improve outcome; they need, however, to be proven in the clinical setting.

The need to improve antiviral treatment options has led to several

Table 1. Currently recommended antiviral agents for patients with weakened immune system and high risk for viral infection or reactivation.

Virus	Treatment, alternative drugs (CDC & NCCN recommended 1.2015)	Disease state (links: further information)
HSV	Acyclovir, famciclovir, valacyclovir	Active therapy, neutropenia, mucositis https://www.nccn.org/store/login/login.aspx?ReturnURL= http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf
VZV	Acyclovir, famciclovir, valacyclovir	Active therapy, neutropenia http://www.rch.org.au/clinicalguide/guideline_index/Chickenpox_varicella/
CMV	Preemptive valganciclovir, ganciclovir	Stem cell transplantation, treatment with alemtuzumab http://www.mayoclinic.org/diseases-conditions/cmv/in-depth/CON-20029514
CMV	Second/third line foscarnet, cidofovir	Resistant CMV (stem cell transplantation, treatment with alemtuzumab) https://www.nccn.org/store/login/login.aspx?ReturnURL= http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf
HBV	Entecavir, tenofovir, lamivudine, adefovir, telbivudine	Resolved HBV infection, HBV antigens, transplantation, anti-CD20/or CD52 therapy http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#b12
HCV	Ledipasvir/simeprevir and sofosbuvir, paritaprevir and ritonavir, ombitasvir and dasabuvir	Transplantation, anti-CD20 therapy, corticosteroids http://www.hcvguidelines.org/full-report-view
HIV	Integrase inhibitors, non-nucleoside reverse transcriptase inhibitors	Chemotherapy, targeted therapy http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0
Influenza A/B	Oseltamivir, zanamivir	Influenza outbreaks (subtype specific) http://www.cdc.gov/flu/professionals/antivirals/antiviral-use-influenza.htm
RSV	Ribavirin	Neutropenia, seasonal pattern http://www.cdc.gov/rsv/clinical/description.html
Adenovirus	Cidofovir	Compromised immune system, seasonal pattern http://www.cdc.gov/adenovirus/hcp/prevention-treatment.html

CDC, Centers for Disease Control and Prevention; NCCN, National Comprehensive Cancer Network; HSV, *Herpes simplex* virus; VZV, *Varicella-Zoster* virus; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RSV, respiratory syncytial virus.

research lines. One important tool that has entered clinical testing and is in constant preclinical refinement is the use of modified cells of the patients' immune system. This option seeks to maximize clearance of the virus, while preserving function of the patients' vital organs that are sensitive to several antiviral as well as antineoplastic drugs. Cidofovir, as we discussed above, is an effective drug that may have serious side effects.

Adoptive immunotherapy

Adoptive immunotherapy is a promising approach in general, and for HSCT recipients in particular. A field where adoptive immunotherapy is particularly important is the growing field of allogeneic cord blood transplantation (CBT).[110] Even though CBT has many advantages over *e.g.*, bone marrow transplantation, immune cells in the cord blood are generally in a more immature developmental state than corresponding cell types in the bone marrow or peripheral blood, which poses a significant risk for recipients with infection. Therefore, several approaches are developed, which include antigen-specific T cells from cord blood, redirecting cord blood T cells using chimeric antigen receptors, and generating cord blood-derived natural killer cells and regulatory T cells.[18,110,111] Recently, cord blood-derived naïve T-cells were exposed to modified antigen-presenting cells, and transduced with the CAR.CD19 retroviral vector, developing thereby a combination of antiviral and antileukemic activity. Specifically these cells could cause lysis of viral antigen–pulsed autologous phytohemagglutinin blasts, demonstrating the capacity to target simultaneously CMV, EBV, and ADV.[112]

At least theoretically, antigen presentation could suffice to direct T-cell responses, and there are multiple methods under development to harness the function of dendritic cells (DC).[113] The importance of antigen-presenting cells was demonstrated with DCs transfected with plasmid DNAs encoding a range of immunodominant and subdominant viral antigens from EBV, CMV, and ADV. These were used to activate T cells that were subsequently expanded in culture. This method had clinical feasibility, as was shown recently, and with an even broader range of encoded antigens. Namely, rapidly generated single-culture virus-specific T cells could recognize 12 antigens from five viruses (EBV, ADV, CMV, BK, and HHV6) on a small patient cohort that had received allogeneic transplants.[114] The group at Baylor College of Medicine had previously described a method by which it is possible to rapidly generate a single preparation of polyclonal (CD4+ and CD8+) T cells which are specific for seven viruses (EBV, CMV, ADV, BK, HHV6, RSV, and influenza virus) frequently described as important risk factors affecting prognosis post HSCT.[115] These broadly virus specific T cells are now been evaluated clinically (ClinicalTrials.gov Identifier NCT01570283).

Still, there is significant room for improvement of methodology for adoptive immunotherapy, which can allow more frequent use. One approach is a combination of regulatory and virus-specific T-cells to increase the efficiency of transferred cells.[116] Another approach is interferon-γ capture of the T cells that are subsequently transferred to the patient: ADV-directed T-cells that were isolated by IFN-γ capture (thereby enriched on the basis of their capacity for IFN-γ secretion) were infused to pediatric HSCT recipients that were also treated with cidofovir.[117] The infusions could clear viraemia; however not all patients clear the infection and some patients die.[109] Therefore it can be concluded that reconstitution of a functional immune response is not under all circumstances possible in HSCT recipients.[117] In part, the need to strengthen the immune system may be also indirectly met by supportive treatment.[118] In fact, supportive treatment may, to some extent, facilitate recovery from viral infections that are potentially dangerous.[118-120]

Agents that target more than one molecular pathway

Finally, an emerging research concept is to assay for pharmaceutical agents that counter viral infections and malignant disease simultaneously, using compounds that inhibit growth of the virus and malignant cells at the same time.[121,122] ALL is not an exception to this option: at Johns Hopkins University an artemisinin-based derivative was developed with a selective toxicity against both ALL cells and CMV, reportedly without to interfere with growth of non-malignant cells.[123] Also chloroquine, which has chemosensitizing activity against some types of malignancy, was shown to improve the cross-presentation of non-replicating influenza virus *in vitro* and T cell responses in mice following a single administration of inactivated virus.[124,125]

Conclusions

From the state-of-the-art in research against viral infections it can be concluded that even though most patients with weakened immune system can benefit from progress in antiviral agents, a viral infection in this patient group still poses a very significant risk. Therefore, preventive measures are very important.

In the case of severely immunocompromised patients such as transplant recipients, patient isolation in a total protective environment could prove an effective means of protection.[126] Direct person-to-person contact including inhalation of respiratory secretions from an affected individual is the primary cause of infections for most viruses. Contact with contaminated surfaces carries also an important risk; however the viability of a virus on contaminated surfaces varies, from the resilient NV that can remain infectious even in small titers, and in the presence of disinfectants, to the unstable RSV that only remains viable for a few hours on hands or surfaces.[127] Therefore well-trained personnel, especially in hand decontamination, and patient isolation, are factors that limit viral complications in patients with a severely weakened immune system.

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