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A New Therapeutic Option for Progressive Multifocal Leukoencephalopathy after Allogeneic Hematopoietic Cell Transplantation

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of central nervous system caused by human polyoma virus, JC virus, which can occur in the patients with severe immune compromised condition. PML is a rare disease, seen in hematologic malignancies, organ transplantation, and HIV infected patients. PML is often fatal, because of the lack of effective anti-viral drug for JC virus. Clinical observations of survival improvement in HIV-positive patients after the introduction of combination antiretroviral therapy (cART) could suggest the importance of restoration of immune response.

In the setting of PML after allogeneic hematopoietic cell transplantation (HCT), it is very difficult to reduce or stop immunosuppressants to restore immune response, because of graft versus host disease (GVHD) and so on. Therefore, new anti-viral drugs against JC virus should be needed. Recently, mirtazapine (antagonists of 5-HT_2 serotonergic receptor) and mefloquine (anti-malarial drug), have been shown to have anti-viral activities against JC virus even in the clinical setting as well as *in vitro* experiments. Several case reports using each drug have been found in recent years. A controlled study for PML patients treated with or without mirtazapine has shown superior survival rate at 1-year in the patients treated with mirtazapine, although statistical significance was not observed. Concomitant usage of both mirtazapine and mefloquine could be expected to induce more effective anti-viral activities, because the mechanism of each drug to inhibit JC virus proliferation is independent. Indeed, some case reports have shown the efficacies of these drugs for the treatment of the patients with PML including after allogenic HCT patients.

Controlled study should be required to identify the efficacies of the combinational treatment of both mirtazapine and mefloquine for the treatment of PML patients after allogenic HCT.

Keywords: Progressive multifocal Leukoencephalopathy; Allogeneic hematopoietic transplantation; Mirtazapine; Mefloquine

Introduction

Progressive multifocal leukoencephalopathy (PML) is caused by the human polyoma virus JC [1]. PML is a demyelinating disease of central nervous system (CNS) resulting from lytic infection of glial cell in severe immune compromised patients and is often fatal.

Basically, PML is a rare disease, seen in only immunosuppressed patients, including hematological malignancies, organ transplant, and patients with chronic inflammatory disorders [2,3]. The prevalence of PML increased substantially during HIV epidemic and mortality related to PML has also increased in the post-HIV era. However, the restoration of immune response by combination antiretroviral therapy (cART) has shown to induce the improvement of prognosis of PML [4]. Recently, immunomodulatory medications which suppress the host cellular immune response, such as nantalizumab for multiple sclerosis and rituximab for malignant lymphoma are associated with PML [5,6].

These results suggested that the restoration of immune response of the patients is crucial to the treatment of PML. However, PML patients after allogeneic HCT could not rapidly reduce nor discontinue the immunosuppressants that are essential to control allo-immune response, such as graft-versus-host disease (GVHD). By contrast, immunosuppressants could be gradually tapered, if complications such as GVHD were well controlled. Then, the improvement of immune response after allogeneic HCT could be expected and would recover the anti-viral activities to JC virus, although it takes quite a few times. Taken together, we could improve the prognosis of PML patients after allo-HCT, if effective anti-viral drugs against JC virus were available. Recently, mirtazapine, antagonist of 5-HT_2 serotonergic receptor and mefloquine, anti-malarial drug, have shown to suppress the JC virus proliferation by independent mechanism. Some case reports would show the efficacies of these drugs on PML patients.

In this review, we discuss the clinical features of PML in the setting of allogeneic HCT and promising combinational treatment with two anti-viral drugs, mirtazapine and mefloquine.

JC Virus

The JC virus is a small ubiquitous DNA polyomavirus with a 5.13 kb circular enclosed double-stranded DNA. The JC virus coding region, which comprises about 90% of viral genome, confers the genotype that is associated with various subtypes that can be found in different geographical areas. But the coding region of JC virus is well conserved and has been convincingly associated with disease pathogenesis. By

contrast, the regulatory region sequence of the JC virus is hypervariable and contains determinants for neurotropism and neurovirlence [7].

After asymptomatic primary infection, which occurs in childhood, the virus remains quiescent in the kidneys, bone marrow, and lymphoid tissues [8-10]. In cross-sectional studies, the JC virus can be detected by PCR in the urine of a third of healthy individuals or immunosuppressed patients with or without PML [11,12]. However, the JC virus is not usually found in the blood of immunocompetent individuals [13].

The JC virus is a neurotropic virus and infects only human beings. Therefore, the absence of animal model has made the research on JC virus pathogenesis difficult for many years. An N-linked glycoprotein with α-(2, 6)-linked sialic acid, present on many human cells, is one of the cellular receptors for the JC virus [14]. In addition, the JC virus can bind to the serotoninergic 5-HT2α receptor to infect astroglial cell in culture [15]. This receptor is present in several cell types, including kidney epithelial cells, B lymphocytes, platelets, glial cells, and neurons [16-18]. Although JC virus receptors are widely expressed and JC virus DNA has been detected in several cells described above, it is difficult to proliferate and maintain the JC virus in human cell culture. These facts have prevented us from investigating pathophysiology of PML and new therapeutic modalities.

Clinical Manifestation and Diagnosis of PML

Classical PML

Clinical symptoms: Typically, PML is caused by productive infection of oligodendrocytes and, to a lesser extent, astrocytes. Therefore, neurological deficits are associated with the areas of demyelination in white matter. As virtually any area of the brain may be involved by JC virus, the presenting symptoms can vary and include muscle weakness, sensory defect, hemianopsia, cognitive dysfunction, aphasia, and coordination and gait difficulties. PML does not usually involve the optic nerve or the spinal cord. Seizures are sometimes observed in PML patients, who had demyelinating lesions immediately adjacent to cortex.

Radiologic findings

MRI or CT scan usually detects the affected brain lesions in the white matter, which do not correspond to specific vascular territories. These lesions appear as hypodense or patchy areas on CT scan, whereas MRI shows areas of hyperintensity on T2-weighted and FLAIR images, and hypointensity on T1-weighted images. Multiple lesions are commonly detected and frequently located in the subcortical hemispheric white matter or the cerebellar penduncles. In every radiographic series of PML, the frontal lobes and parieto-occipital regions appear to be most commonly affected, presumably as a consequence of their volume. In some cases, PML lesions can also be found in grey matter structure such as the basal ganglia or the thalamus, because there are myelinated fibers in these structures. In classic PML lesions, edema, mass effects, or contrast enhancement on imaging usually is not observed [19].

Diagnosis

The detection of viral DNA or proteins by in situ hybridization or immunohistochemistry on a brain biopsy sample or of JC virus DNA in CSF by PCR is essential to the diagnosis of PML. For definitive diagnosis of PML, neuropathologic demonstration of the typical histopathologic triad (demyelination, bizarre astrocytes and enlarged oligodendrocyte nuclei) should be required. Histologically, PML is characterized by a productive, lytic infection of oligodendrocytes and astrocytes, leading to multiple areas of demyelination in the CNS. In addition, there can be reactive gliosis and giant, bizarre multinucleated astrocytes in affected areas. However, cases with typical and radiological presentation might be diagnosed as possible PML even without JC virus detection in CFS. But it is required to rule out other causes of infection or tumors [20].

Prognosis

PML is still a fatal disease with no specific disease. In HIV-positive patients with PML, the prognosis has been improving since the introduction of cART. Recent reports have shown that recovery of immune response induced by cART improve the prognosis in HIV-positive patients with PML [21,22].

In the patients after allogeneic HCT, the prevalence of PML still remains unclear, although the prognosis has been thought to be fatal.

PML-IRIS

Although a cellular immune response directed against the JC virus is beneficial in PML patients, a rapid global recovery of immune system might not always be favourable. Such a situation can trigger an immune reconstitution inflammatory syndrome (IRIS), which is an inflammatory response to pathogens associated with recovery of immune system after period of immune suppression [23,24]. This immune reconstitution is inferred by an increase in T-lymphocyte counts after the initiation of cART in HIV-positive patients and the reduction or cessation of immunosuppressive therapy in the patients after allogeneic HCT or organ transplantation.

Clinical presentation

Typically, PML-IRIS can be diagnosed when HIV-positive patients who are treated with cART subsequently have increased functional CD4+ T cells and decreased HIV viral road in plasma. In HIV-negative patients, IRIS might also develop after restoration of cellular immune response induced by the reduction of immunosuppressants. The restoration of immune response induces the development of inflammatory PML or an inflammatory reaction at a site of previously diagnosed PML lesions. This inflammatory reaction is characterized by contrast enhancement or edema of PML lesions on MRI with possible mass effects, and is associated with acute and usually transient clinical worsening not consistent with the expected course of previously or newly diagnosed PML [25].

Radiologic findings

Contrast enhancement might be detected on MRI, due to the local inflammation and breakdown of the blood-brain barrier in both HIV-positive and HIV-negative patients with PML-IRIS. This inflammation can be associated with brain edema, swelling, and mass effects, in the most severe cases, can cause brain herniation and death [26]. However, contrast enhancement might not necessarily be observed at the time of MRI evaluation, because it might be a transient event.

Host immune response

As described above, immune response to JC virus is closely associated with the reactivation of JC virus and the occurrence of PML. To date, immune responses to JC virus in the patients with PML have been extensively examined.

The prevalence of antibody formation against the JC virus has been suspected to vary from 40% to 85% in western countries. Compared with healthy controls, the JC virus-specific antibody titers in both HIV-positive and HIV-negative patients with PML were increased. But the increases of antibodies do not prevent the occurrence of PML in these patients. Furthermore, although JC virus-specific antibody becomes detectable in CSF with JC virus clearance after treatment with cART in HIV-positive patients with PML, neither the presence of intrathecal nor serum JC virus-specific antibodies prevent the onset of PML. Therefore, in these patients, the JC virus-specific antibodies produced by the humoral immune response alone are not sufficient to prevent reactivation of JC virus, leading to PML [27,28].

These results lead to the expectation that the cellular immune response is necessary for preventing from viral reactivation and proliferation. In fact, JC virus-specific CD4+ T cells have been detected in the blood of patients who survived PML and the number of these cells correlates with JC virus clearance from the CSF [27,29]. The role of CD8+ cytotoxic T cells (CTL) has been studied in detail. JC virus-specific CTLs are usually detected in the blood of PML survivors and rarely in patients with PML who have fatal outcome within 1 year from disease onset [30]. In a prospective study, 13 of 15 patients with PML who had detectable JC virus-specific CTL in the early period after symptom onset had inactive disease during follow-up, whereas 9 of 11 patients who did not have such a response continued to have an active disease [31]. In addition, CD8+ T cell are major inflammatory cells found in PML lesions, where they aggregate around infected cell [32].

Immune responses in immunocompromised patients are closely related to the reactivation of JC virus and the occurrence and prognosis of PML. Therefore, it is a key point to treat PML to restore the immune responses in HIV-positive patient and to regulate in HIV-negative patients, especially the patients who received allogeneic HCT or organ transplantation. However, the cessation or decrease of immunosuppressants would restore immune responses to JC virus but increase the risk to induce GVHD or organ rejection. In the setting of allogeneic HCT, immunosuppressants such as cyclosporine A and tacrolimus could be gradually decreased and stopped, if GVHD was well controlled, although it takes various period in each case. Gradual reduction of immunosuppressive therapy could impair immune responses of T-lymphocytes to JC virus and might induce reactions similar to IRIS.

Treatment for the patients with PML who received allogeneic HCT

The current goal in PML treatment is to restore the host adaptive immune response to the JC virus for control of the infection, because there have been no specific antiviral drug against the JC virus. In HIV-positive patients, this goal is mainly accomplished by cART therapy.

As shown in Table 1, 15 cases with PML after allogeneic HCT have been reported. Median of patient age was 38 years old (range: from 2 months to 65 years). Source of stem cell was as following; 7 related peripheral blood, 2 related bone marrow, 3 unrelated bone marrow, and 4 cord blood. The prophylaxis for GVHD were various. In 13 of 15 cases, PML was developed from 6 to 18 months after allogeneic HCT. 7 patients were diagnosed by PCR for JC virus in CSF and 5 patients by brain biopsy. In the patients who received allogeneic HCT, the only therapeutic option is thought to reduce immunosuppressive drugs, enabling to repair the immune system to control the JC virus infection. However, the reduction of immunosuppressants would induce worsening of GVHD and/or various complications derived from allogeneic immune reactions. Conversely, severe immunosuppression for GVHD and/or complications might induce viral reactivation and the occurrence of PML. In 7 of 15 patients, the complication with GVHD was described and 6 of 7 patients with GVHD were treated with additional steroid administration. In these conditions, it is very difficult to reduce immunosuppression in response to the occurrence of PML in the patients receiving allogeneic HCT.

The presence of JC virus-specific cytotoxic T-lymphocytes (CTL) was associated with a trend toward better prognosis in several reports. Balduzzi et al. reported that they generated donor-derived JC virus antigen-specific CTLs *in vitro* for the treatment of PML patients who received allogeneic HCT [41]. Adaptive infusion of these CTLs resulted in the clearance of JC virus-DNA in the CSF and remarkable improvement. The report of Buckanovich et al. has shown the possibility of donor lymphocyte infusion [35]. In 3 of 4 patients treated with DLI or CTLI, the improvement of PML symptoms was observed (Table 1). But it is generally impossible to generate JC virus-specific CTLs or infuse donor-derived lymphocytes in every case with PML in clinical setting. In fact, we could not be able to generate CTLs if the source of allogeneic HCT is unrelated donor or cord blood.

Reference	Age/gender	Pre-transplant diagnosis	Stem cell source	Immuno suppression	Onset from transplant	Diagnosis	Treatment	Outcome
Owen et al. [33]	43/male	CML	rPB	CsA, MTX, Campath1	17 months	MRI	cytarabine	Death, 2 months
O'Shaughnessy et al. [34]	44/female	CML	uBM	CsA, MTX, Campath1	5 months	Brain biopsy	cytarabine	Death, 3 months
Buckanovich et al. [35]	29/female	ML	rPB	CsA	6 weeks	MRI	IL-2, DLI	Alive, unknown
Steurer et al. [36]	32/male	ML	rPB	CsA	17 months	Brain biopsy	IL-2, cytarabine, cidofovir	Death, 3 months
Focosi et al. [37]	33/female	ALL	rPB	unknown	6 months	PCR (CSF)	risperidone	Alive, 3 months

Karfan-Dabaja et al. [38]	51/male	ML, MDS	uBM	Tac, MTX	5 months	Brain biopsy	cytarabine	Death, 5 months
Karfan-Dabaja et al. [38]	41/male	ML	rPB	Tac, MTX	6 months	PCR (CSF)	Withdrawal of Tac	Death, 1month
Pelosini et al. [39]	30/female	ALL			17 months	Brain biopsy	cytarabine, cidofovir, ganciclovir, risperidone, DLI	Alive, 19 months
Yasuda et al. [40]	2mo/male	WAS	uBM	CsA, MTX, PSL	6 months	PCR (CSF)	Acyclovir, rivabirin, INF-alpha, DLI	Death, 2 months
Balduzzi et al. [41]	19/male	ALL	rBM	CsA, MMF, CY, MTX, rituximab	60 months	PCR (CSF)	cidofovir, citalopram, CTLI	Alive, 26months
Sheikh et al. [42]	38/female	AML	CB	Tac, MMF	10 months	Autopsy	Withdrawal of steroid	Death, 2 months
Kishida et al. [43]	37/male	AML	CB	Tac	8 months	PCR (CSF)	mefloqine	Alive, 20 months
El-Cheikh et al. [44]	59/female	ML	CB	CsA, MMF	10 weeks	PCR (CSF)	cidofovir, mirtazapine, mefloqunie	Death, 1 month
Kafman at al. [45]	65/male	ALL	rBMT	unkown	11 months	Brain biopsy	No therapy	Death, 1month
Yoshida et al. [46]	40/female	MF	rPB	CsA, MTX	10 months	PCR (CSF)	mirtazapine, mefloqunie	Alive, 49months

CML: Chronic Myelogenous Leukemia; ML: Malignant Lymphoma; MDS: Myelodysplastic Syndrome; ALL: Acute Lymphocytic Leukemia; WAS: Wiskott Aldrich Syndrome; AML: Acute Myelogenous Leukemia; rPB: Related Peripheral Blood Stem Cell; rBM: Related Bone Marrow; uBM: Unrelated Bone Marrow; CB: Cord Blood; CsA: Cyclosporine A; MTX: Methotrexate; Tac: Tacrolimus; IL-2: Interleukin-2; DLI: Donor Lymphocyte Infusion; INF: Interferon; CTL: Cytotoxic T Lymphocyte Infusion

Table 1: PML in recipients of allogeneic SCT.

After allogeneic HCT, we have found difficulties to collect brain biopsy samples or CSF because of pancytopenia and so on, when PML has been suspected. In this condition, it might be necessary to start the treatment for PML at possible PML diagnosis.

In general, it is difficult to rapidly restore the immune response after allogeneic HCT, but it is possible to gradually reduce the immunosuppression if complications such as GVHD were tolerably controlled. Therefore, antiviral drugs are required to inhibit JC virus proliferation, at least in the periods during the reduction of immunosuppressants, in the setting of allogeneic HCT.

Anti-viral drugs against JC virus

There has been no specific antiviral drug against the JC virus. But several antiviral therapies for the treatment of PML have been previously investigated.

Cidofovir

Cidofovir, an antiviral drug against human cytomegarovirus, initially showed promising results to improve survival of HIV-positive patients with PML in combination with cART in two observational studies [47,48]. However, a multicohort analysis of efficacy of cidofovir treatment for the patients with PML showed no survival benefit for the patients who received cidofovir [49].

Cytarabine

Cytarabine is primarily a chemotherapeutic agent that inhibits JC virus replication *in vitro*. In a retrospective analysis, cytarabine is associated with stabilization of PML in 7 of 19 patients with leukemia or lymphoma. However, other two studies of the efficacy of an antiviral therapy using cytarabine for the HIV-positive patients with PML could not show any survival benefits [50,51].

New anti-viral drugs against JC virus

Mirtazapine

Elphick et al. reported that JC virus uses the 5-HT2A receptor to infect cultured cells and antagonists of 5-HT_2 serotonergic receptor, such as chloropromazine and clozapine significantly inhibited the infectivity of glial cells by the JC virus in 2004 [15]. These results have promoted the use of mirtazapine, a serotonine reuptake inhibitor for the treatment of PML. In facts, a favorable outcome in PML patients treated with mirtazapine has been described in several case reports [52,53]. However, there is still no clear evidence of efficacy. Marzocchetti et al. reported the controlled study of mirtazpine for the treatment positive- and negative PML patients. Fourteen patients with PML (7 HIV-positive and 7 HIV-negative patients) were treated with mirtazapine of 15-45 mg at bed time within 1 year after PML diagnosis until the end of observation or death. Untreated group consisted with 11 patients with PML (6 HIV-positive and 5 HIV-negative patients)

who were not receiving any treatment except cART, matched for CD4 count and HIV viral load. The 1-year survival rate was 62% in patients treated with 5HT2A receptor blockers versus 45% untreated patients, but no significant difference was observed (p=0.45) [54].

Mefloquine

To identify drugs with anti-JC virus activity, Brickelmaier et al. screened 20,000 approved drugs and biologically active molecules for their anti-JC virus activities in an *in vitro* infection assay. They identified a number of different drugs and compounds that had significant anti-JC virus activities and micromolar concentration and lacked cellular toxicity. Of these, mefloquine, an anti-malarial drug, has been to achieve efficacious concentrations in the brain. Mefloquine inhibits viral DNA replication in infected cells, but does not inhibit the entry of JC virus to glial cells [55].

As same in mirtazapine, several case reports have shown a favorable outcome in HIV-positive and HIV-negative patients with PML [56-60], even in the setting of allogeneic HCT (Table 1) [43]. But there have been no large scale clinical trials using mefloquine for the treatment of PML. The efficacies of mefloquine for PML have not been determined yet.

Combined treatment with mirtazapine and mefloquine for the treatment of the patients with PML

Both mirtazapine and mefloquine have been shown to have anti-JC virus activities in *in vitro* data. In clinical setting, there have been several case reports to expect the efficacies for the treatment of the patients with PML, although there have been still no clear evidence.

Each drug has independent mechanisms to inhibit the proliferation of JC virus. Mirtazapine inhibits the entry of JC virus into glial cells via serotonergic receptor [15]. In contrast, mefloquine inhibits the viral DNA replication in infected cells [55]. Therefore, combinational usage of both mirtazapine and mefloquine could introduce either additive or synergistic effects on the treatment of PML patients.

PML patients who treated with combinational therapy both mirtazapine and mefloquine, are listed in Table 2. All of patients were diagnosed by the detection of JC virus using brain biopsy or PCR in CSF. In 7 of 9 cases, combinational therapy of mirtazapine and mefloquine has been reported to be effective, although dosage of each drug has been varied. The median of observation period for 7 improved patients was 12 months (range; from 11 days to 51 months). In these reports, underlying diseases were various but these results could suggest the possibilities to control PML even under the compromised conditions. In two cases after allogeneic HCT, no efficacy was observed in one case but long-term effectiveness in another case. However, previous reports would suggest that this combinational treatment with mirtazapine and mefloquine has the possibilities to inhibit JC virus proliferation during the period which is required for the tapering immunosuppressants. Then, it could be expected the efficacies of combinational therapy of mirtazapine and mefloquine even in allogeneic HCT patients.

Although mirtazapine is primarily a drug for depressive disease and widely used in many countries, no severe side effect has been reported. Mefloquine is anti-malarial drug, which is safely used for the prevention of malaria. In fact, no severe adverse effect has been reported in the treatment with mirtazapine and mefloquine.

Reference	Age/gender	Underlying disease	Diagnosis	Dose of mirtazapine	Dose of mefloquine	Outcome
Kurmann et al. [61]	56/male	CVID	PCR (CSF)	30 mg/day	250 mg/week	Stable, 23 months
Epperla et al. [62]	77/male	CLL	Brain biopsy	30 mg/day	250 mgx3 days then 250 mg/week	Improve and stable, 24 months
Di Pauli et al. [63]	58/female	CLL	Brain biopsy	30 mg/day	250 mg/week	Death, 3.5 months
Yoshida et al. [46]	40/female	MF, post allo-SCT	PCR (CSF)	15 mg/day	1100 mg at first day then 275 mg/week	Improve and stable, 51 months
Christakis et al. [64]	69/male	Diabetes mellitus	Brain biopsy	30 mg/day	250 mgx3 days then 250-500 mg/week	Improve and stable, 12 months
Moenster et al. [65]	49/male	HIV	PCR (CSF)	30 mg/day	250 mgx3 days then 250 mg/week	Significant improvement, 11 days
McGuire et al. [66]	74/male	CD8+ T lymphocyte deficiency	PCR (CSF)	15 mg/day	250 mgx3 days then 250 mg/week	Stable, 11months
Schroder et al. [67]	41/female	MS	PCR (CSF)	60 mg/day	250 mgx3 days then 250 mg/week	Improve and stable, 3 months
El-Cheikh et al. [44]	59/female	ML, post allo-SCT	PCR (CSF)	unknown	unknown	Death, 1 month

CVID: Common Variable Immunodeficiency; CLL: Chronic Lymphocytic Leukemia; MF: Myelofibrosis; MS: Multiple Sclerosis

Table 2: Combinational therapy with mirtazapine and mefloquine for the patients with PML.

Taken together, this combinational treatment with mirtazapine and mefloquine could be safe and expectedly effective for PML in the setting of allogenic HCT patients. Early or prophylactic introduction of this treatment would be more effective, when PML was suspicious, especially in severe immunosuppressive state such as steroid therapy for GVHD.

Conclusion

PML has been rare but still considered to be fatal disease, especially in the patients with PML after allogeneic HCT, although the prevalence of PML in this setting still remains uncertain. However, the improvement of survival in the HIV-positive patients with PML after the introduction of cART would provide the possibilities to make the prognosis of the PML patients after allogeneic HCT better, if we could inhibit the proliferation of JC virus until the immune response could recover. In the patients after allogeneic HCT, immunosuppressive agents, such as cyclosporine A and steroid, could be tapered if GVHD and other complications were well controlled.

Recently, new anti-viral agents against JC virus, mirtazapine and mefloquine, have been expected to be effective for the treatment of PML. The combinational usage of both mirtazapine and mefloquine could be more effective than single usage of each drug, because each drug has independent mechanism to inhibit JC virus proliferation. Indeed, several case reports have shown the effectiveness of the combinational treatment of both drugs, but the dosage of these drugs and the duration of the therapy were varied. Therefore, controlled study should be required to identify the efficacy of the combinational treatment of both mirtazapine and mefloquine.

In this review, we have shown the possibilities to improve the prognosis even after allogeneic HCT by the combinational treatment with both mirtazapine and mefloquine, following the tapering of immunosuppressants as possible as we can.

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