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Treatment of HIV-Related Primary Central Nervous System Lymphoma with AZT High Dose, HAART, Interleukin-2 and Foscarnet in Three Patients

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Abstract
Purpose: Combined immunomodulatory and antiviral treatment was administered to three patients with newly diagnosed HIV-associated primary central nervous system lymphoma (PCNSL) in an attempt to improve outcomes.
Patients and methods: Three patients from our institution who were recently diagnosed with HIV-associated PCNSL received intravenous azidothymidine (AZT) 1.6 gr. bid for two weeks, followed by oral AZT 250mg bid from day 15. In addition, complementary highly active antiretroviral therapy (HAART) with a second nucleoside reverse transcriptase inhibitor (NRTI) plus one protease inhibitor (PI) and interleukin 2 (IL-2) subcutaneously 2 million units twice daily (bid) plus foscarnet 90mg/kg bid were administered on days 1-14. One patient received anti-Epstein-Barr virus (EBV)-maintenance therapy with ganciclovir, followed by cidofovir [1].
Results: All patients experienced progressive disease while on induction therapy, and switched early to whole-brain radiation therapy (WBRT) as second line-treatment. No grade 3 or 4 toxicities were observed. Two patients died on days 50 and 166 respectively due to progressive disease. The third patient with histologically proven lymphoproliferation and only suspected PCNSL remained alive at 53 months. He was on HAART and remained clinically and neurologically stable.
Conclusion: Although IL-2, HAART, high-dose AZT and foscarnet are used for other HIV-related conditions, they did not demonstrate benefit in lymphoma remission for 2 HIV- associated PCNSL patients. The third patient went into delayed remission after additional radiotherapy and was in good clinical and neurological health status over 53 months after diagnosis.

Introduction

HIV-associated PCNSL remains difficult to treat. HIV infection induces a deficient immunologic milieu that enables other oncogenic viruses such as EBV to escape immune control in a multifactorial way, which can lead to the onset of lymphoma [2]. The incidence of HIV-related PCNSL has decreased since the widespread introduction of HAART [3]. Presentation of the disease is more frequent in persons with reduced performance status, CD4-counts below 100/µl and high HIV viremia levels [4, 5, 6].

In immunocompetent populations, outcome and toxicity of different therapy regimens are largely age-dependent. Significantly reduced survival and neurotoxicity rates of up to 90% occur with combined chemotherapy-radiation regimens in the above 60 year age group. In all age groups, combination radiochemotherapies, with mostly intrathecal (it) administration of methotrexate (MTX) and/or cytarabine, prolong overall median survival rates by up to 55 months [7-9]. However, they can cause increased treatment-associated mortality, with high rates of infection and neurotoxicity. Intensive chemotherapy-only regimens show less neurotoxicity with similar survival rates [7-10]. Higher response rates are obtained with intensive autologous stem-cell-rescue protocols [11-14].

In contrast to therapeutic success demonstrated for immunocompetent patients, the outcome of HIV-associated PCNSL is still considered poor [6,15]. Median survival rates range from four to six weeks with best supportive care alone and 3 to 5 months with cranial radiation treatment [4, 15-17]. Most HIV-positive PCNSL patients are in clinically poor condition, and have advanced immunosuppression. Moreover, HIV-associated leukoencephalopathy in advanced HIV disease is frequent, considering that neurotoxicity is one of the most frequent debilitating side effects in combined chemo-radiotherapy protocols.

HAART induced immune recovery improves survival of patients with AIDS-associated PCNSL and systemic lymphoma, but these patients still have reduced overall survival along with higher treatment-related mortality than HIV-negative patients [4, 6, 15, 18, 19]. The highest survival rates were reported in a German survey with HAART and radiotherapy 40Gy

(n = 5/6) or hdMTX/40Gy (n = 1/6) of more than 18 months. Steroids had no prognostic benefit and most PCNSL-patients (n = 23/29) were not eligible for any treatment [4]. HAART has been used alone for HIV-related PCNSL in patients with poor clinical status, patients who have declined other therapies, and in those experiencing failing therapies. The impact of curative HAART of HIV related PCNSL has been reported in five single cases [20-23].

Antiviral and immune-based therapy of HIV-related PCNSL was suggested by Raez et al. [1]: 5 ART-naive HIV-positive patients diagnosed with PCNSL were treated with ganciclovir, AZT and interleukin-2 for two weeks and ganciclovir maintenance therapy. Long lasting remission and a marked response after two weeks of treatment was reported in four out of five patients: two patients were alive and disease-free 22 and 13 months later, one died at month seven due to sepsis, one died after four months with progressive disease, and one patient was lost to follow-up in partial remission after changing to radiation-therapy due to CTC grade 4-neutropenia and thrombocytopenia at week four. Aboulafia, et al. [5] adopted a similar treatment strategy with one out of four patients remaining in complete remission after more than four years of follow-up.

We report three patients who were treated at our institution following a modified treatment plan originally published by Raez.

Methods - 3 Case Reports

Doses and regimens: Intravenous AZT 1.6 gr. bid on days 1-14, then oral AZT 250mg bid from day 15; ongoing HAART with one additional NRTI as HAART-backbones, plus one protease inhibitor (lopinavir/ritonavir or nelfinavir according to individual conditions), orally bid in standard doses; IL-2 subcutaneously two million units bid at days 1-14; foscarnet bid 90mg per kilogram body weight on days 1-14 in conjunction with one litre of saline bid to prevent renal failure. Maintenance therapy with foscarnet (alternatively ganciclovir or cidofovir in one patient) was administered according to patient clinical status and individual toxicities.

In case of clinical or radiological disease progression, standard therapy with radiation and ongoing HAART was started immediately. Cerebral computerized transaxial tomography (CTT) scan controls were performed on days 7 and 14 after the start of treatment, unless there was clinical deterioration, when CCT scans were performed earlier.

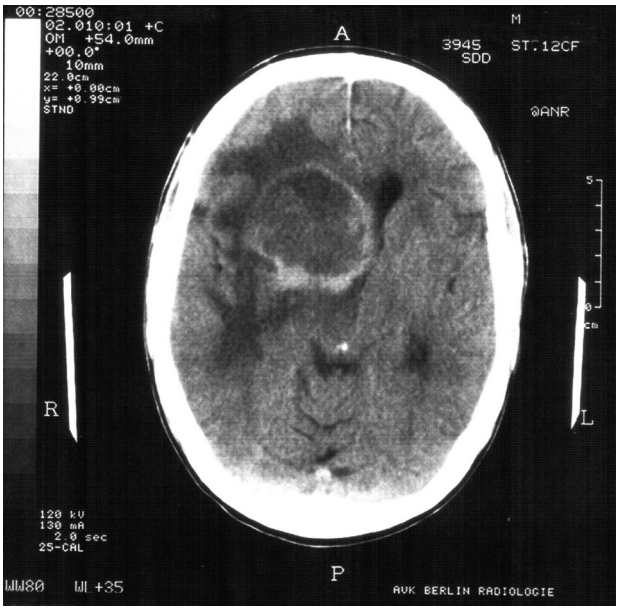
The protocol was presented to the German Working Group for HIV-associated lymphomas. All patients underwent a brain biopsy that showed large B-cell lymphomas of high malignancy in two patients and lymphoproliferative disease with a large amount of necrotic tissue that was highly suspicious for NHL in the third patient despite lack of proven monoclonality. Staging results for systemic lymphoma resulted negative.

A treatment plan was adapted and proposed according to each patient's clinical status, and informed consent was obtained.

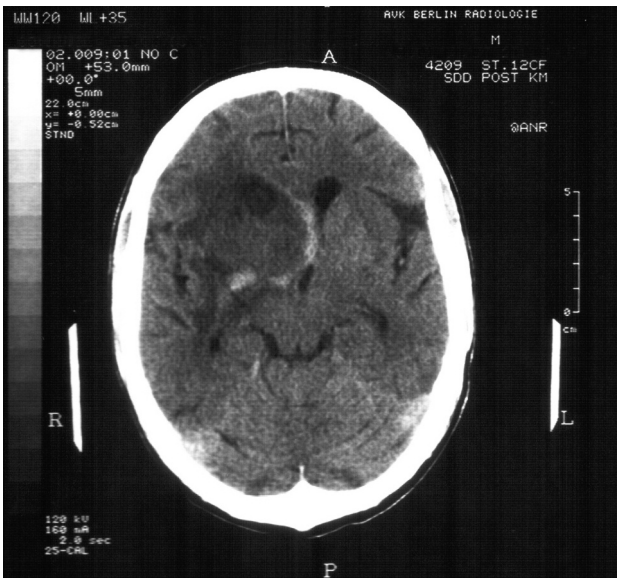
Results

Patient 1

Patient 1 was a 33-year-old MSM male, who had been diagnosed HIV-positive since 1995. His CD4-count was 16/µl and at the time lymphoma diagnosis, he was ART-naive. He also had clinical signs of Kaposi-sarcoma with lesions on skin, tongue, palate and glans penis that had been treated for four months with systemic liposomal doxorubicin.



Pat. 1 at treatment start.



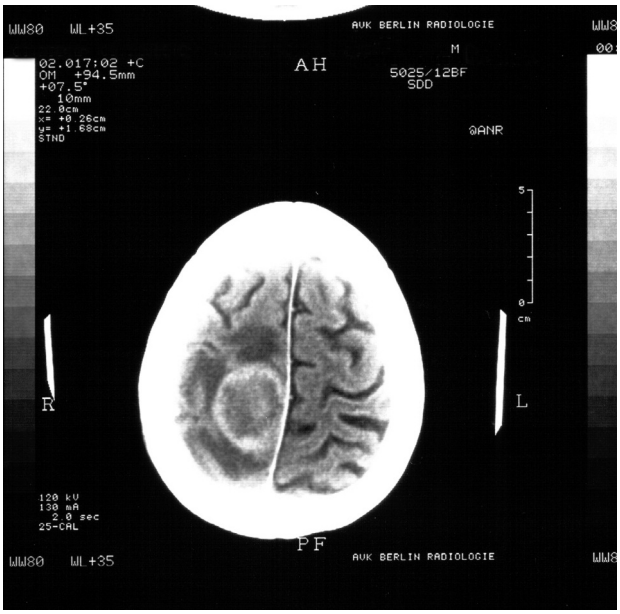
Pat. 1 after 2 weeks of treatment with IL-2, AZT, HAART, Foscarnet.

He had undergone hospitalization for pneumocystis carinii pneumonia, which had been treated successfully four weeks prior to the lymphoma diagnosis. This was followed by three weeks of ongoing treatment for histologically proven pulmonary tuberculosis and oral candidiasis. Subsequently, a 5 cm lesion in the basal ganglia with extensive perifocal oedema was demonstrated by CCT scan, which had been performed because of a history of headaches and grand mal seizures. A presumptive diagnosis of cerebral toxoplasmosis was made, and empiric anti-toxoplasmosis therapy was initiated. After one week of treatment, the tumour diameter increased. A stereotactic brain biopsy was performed and revealed a highly malignant, large B-cell lymphoma (LCA pos., CD20 pos., Prol.-MIB-1 50%, CD30 neg., EBV-markers not performed).

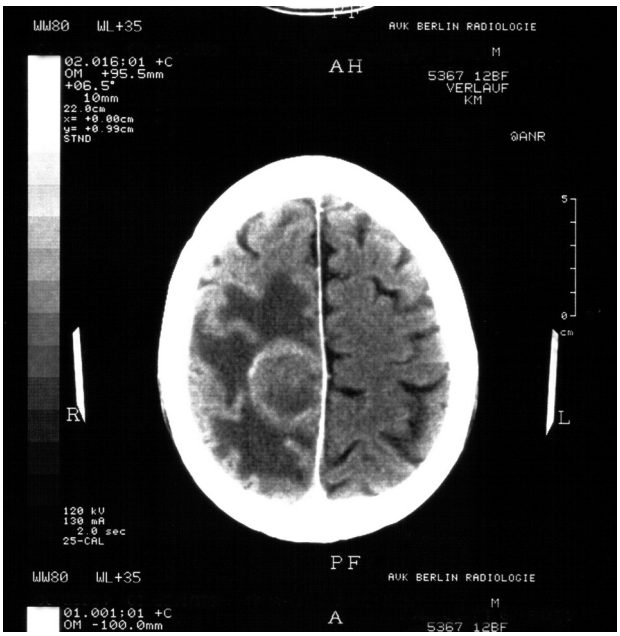
The patient was treated for 13 days according to the aforementioned treatment plan concomitant to his anti-tuberculosis therapy (isoniazid, rifampicin, ethambutol, pyrazinamide), which was well tolerated. High dose AZT, lamivudine and saquinavir boostered by ritonavir were selected for the HAART regimen. Due to increased intracranial pressure, dexamethasone 24mg/day was added. Tumour regression could not demonstrated by CCT scan on days 7 and 13, so whole brain radiotherapy (WBRT) was initiated. Follow-up immune status was not performed. After a cumulative dose of 20 Gray, WBRT was interrupted because of clinical deterioration. The dexamethasone dose was raised to 80 mg/day. The patient expired due to lymphoma progression after discharge to his home, 50 days after diagnosis and 80 days after onset of signs and symptoms.

Patient 2

Patient 2 was a 23-year-old IVDU male (men sex female), who had been diagnosed HIV-positive for two years (CD4-count 50/µl, 13%, Ratio 0.2, ART-naïve, HIV-viral load 522.600 c/ml). He had a history of wasting syndrome, chronic hepatitis C and paranoid psychosis. He was hospitalized for a 2 month exacerbation of the chronic paranoid psychosis and fever of unknown origin. A diagnosis of systemic cryptococcosis, manifested with fever, elevated serum-titre of 1 : 40/1 : 320 and repeated negative CSF-findings, was confirmed 2 months before the PCNSL diagnosis. He was treated with fluconazole, which resulted in clinical resolution of the cryptococcosis. He had also been diagnosed with pneumonia due to S.pneumoniae, 6 weeks before the PCNSL diagnosis, and was successfully treated with IV ampicillin/sulbactam. Two weeks later, due to a 2 cm contrast enhancing cerebral focus, empiric toxoplasmosis therapy was initiated for 2 weeks. The patient developed left sided paralysis and CCT scan revealed that the cerebral focus had developed into a rapidly growing 4 cm parietal mass with accompanying oedema, and normal cytological, HSV-consensus-PCR and microbiological CSF findings. Brain biopsy demonstrated an EBV-associated diffuse large B-cell-lymphoma (CD20+, MIB-1 60%, LMP+). The initial tumour growth appeared to stop after one week with the aforementioned treatment plan, which included HAART with lamivudine and nelfinavir.



Pat. 2 at treatment start.



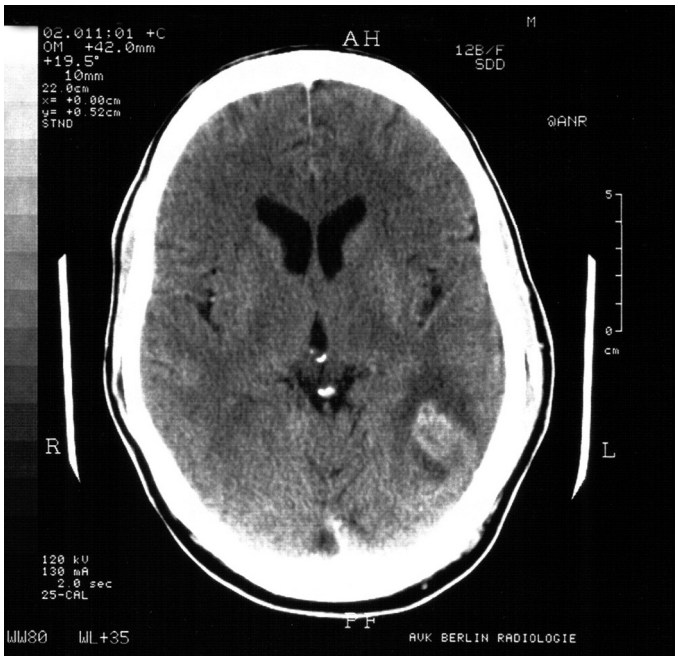
Pat. 2 after 2 weeks of treatment with IL-2, AZT, HAART, Foscarnet.

However, over the total course of three weeks tumour size progressed to 5 cm with a slight midline shift. His CD4-count increased two weeks after initiation of HAART and IL-2 to 810/µl (52%, CD4/CD8 ratio 1.5), and HIV-viral load decreased to 1840 copies/ml. Radiation therapy (40Gy) was initiated followed with concomitant dexamethasone. Slight partial tumour regression was observed on day 11 after start of radiation therapy. However, the patient had minimal signs

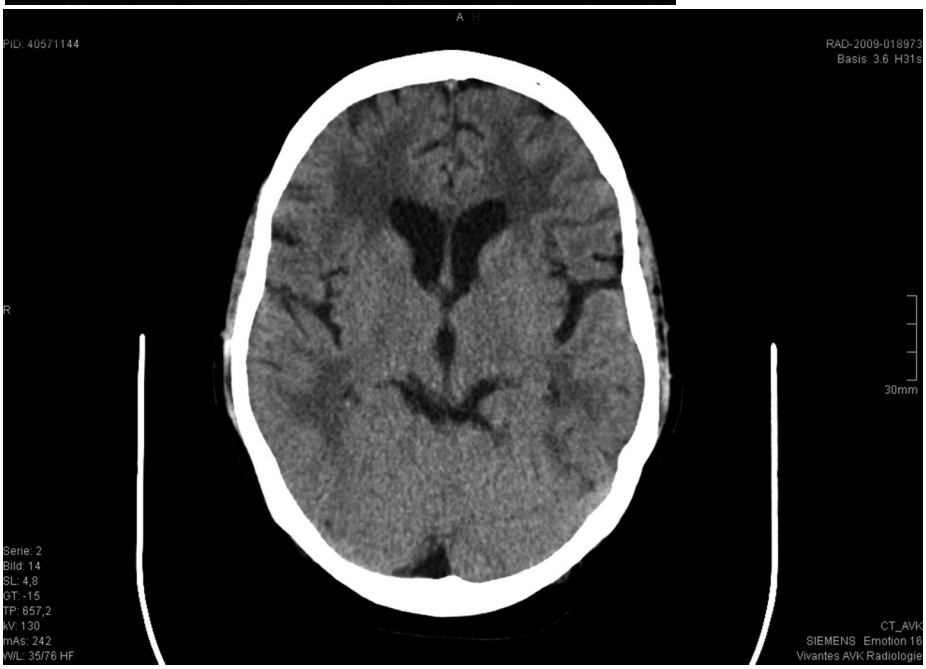
of improvement of the left sided paralysis and severe psychosis. Despite support by nurses in hospice care, medication adherence was inadequate due to the severe psychosis. He continued to worsen clinically, and expired due to lymphoma progression on day 166 after initial lymphoma diagnosis, and 200 days after the onset of signs and symptoms.

Patient 3

Patient 3 was a 44-year old male (men sex male), who had been diagnosed HIV-positive for 7 years (CD4-count 120/µl, CD4/8-ratio 0.2, viral load 793.000 copies/ml; ART-naïve). He had a history of seasonal allergies, primary syphilis, gonorrhoea, and condylomata accuminata. He was hospitalized after a first grand mal episode. A CCT scan revealed a contrast-enhancing temporal mass with a diameter of 1.2cm accompanied with perifocal oedema. The spinal fluid was HSV-consensus-PCR negative. Despite one week of empiric toxoplasmosis therapy, the mass had expanded to a diameter of 2cm. Stereotactic brain biopsy showed an EBV induced lymphoproliferation (LMP+, EBNA-2+, CD30-, CD20+, high proliferation-index KI-67). Due to the presence of massive necrosis and high proliferation index, highly malignant lymphoma was suspected, but could not be confirmed with the biopsy specimen material. Since a repeat biopsy would have put the patient at further risk, these highly suspicious results were deemed consistent with the clinical presentation, and treatment was initiated with foscarnet, interleukin-2, high dose AZT for 18 days, with lamivudine and lopinavir/ ritonavir bid added for HAART in standard doses. Due to a second



Pat.3 at treatment start.



Pat.3 after 5 years of treatment with IL-2, AZT, HAART, Foscarnet.

seizure on day 7, gabapentin, which had been administered since the first seizure, was raised from 1200mg to 2100mg daily. There was no change demonstrated by CCT scan.

Overall, he tolerated the treatment regimen well except for limb edema, which improved with xipamid 10mg, and one episode of local induration at an interleukin injection site that resolved without sequelae. A CCT scan on day 18 showed a tumor diameter of 2.5-3cm with no change in perifocal oedema. There were no signs of compression. His CD4-count on day 11 was 550/μl, CD4/CD8 ratio 2.0, and on day 30 it was 180/μl, with a ratio of 0.7, and a viral load of 790 copies/ml. HAART (AZT, 3TC, LPV/r) was continued, and ganciclovir maintenance therapy (once daily 5mg per bodyweight) was initiated. Forty two days after treatment initiation, the patient underwent whole brain radiotherapy with a 30 Gy cumulative dose. Six months after start of treatment, his HIV viral load was constantly below detectable levels, and after 4 months, CCT scan showed CR with leukencephalopathy. After completion of 3 months of ganciclovir maintenance therapy, the patient received cidofovir monthly for one year after the induction period (cumulatively 20 times) against EBV proliferation because of his relatively low CD4-count (nadir 100/μl after 6 months). The cidofovir was then discontinued due to a steadily improving immune response (CD4-count 306/μl). Ophthalmological and neurological examinations as well as renal function tests were within normal limits 2 years after the start of treatment. Four years from time of diagnosis, CCT restaging demonstrated constant marked demyelinization of the cerebral medullary layer, which was most likely radiotherapy-associated. The patient has been clinically and mentally stable 53 months after diagnosis. He remained on HAART with AZT, 3TC, LPV/r with CD4-counts above 300/μl and without a detectable viral load. A year after diagnosis the patient retired from work.

Overall Results

Combined first-line therapy with HAART, IL-2, foscarnet and AZT-high-dose was not effective in reducing tumour growth in the 3 patients. Therefore, standard radiation therapy was indicated after 2 weeks of therapy in all patients. After 4 months of radiation therapy, patient 3 showed a complete remission of the tumour mass 53 months after diagnosis and a stabilized immune response by HAART as well as cidofovir maintenance-therapy (20 cycles). However, only EBV-lymphoproliferation was proven histologically. Lymphoma was suspected because of the high proliferation index and necrotic tissue masses. Retrospectively, based upon the positive response to radiation and absence of an early response to immunomodulating therapy, a diagnosis of lymphoma (or a preliminary stage of it) was likely.

The two-week course of therapy in the 3 patients was well tolerated. Adverse events including hematological drug reactions were few and resolved with minimal treatment. There was no common toxicity criteria (CTC) grade 3 or 4 toxicity.

Discussion

Although these case reports shared comparable clinical characteristics to those treated by Raez et.al. [1], they did not have similar results despite having received optimized antiviral medication with foscarnet instead of ganciclovir and demonstrating excellent immune responses in 2 of the 3 patients (patient 1 was not evaluated for an immune response). Combined therapy with IL-2, AZT, foscarnet and HAART had no effects on reducing tumour growth in our ART-naive HIV-positive patients with PCNSL in the short time of administration. By comparison, this differs from Raez et.al, who reported at least partial remission within two to three weeks in 4 out of 5 patients.

These case reports suggest that this was probably due to rapid PCNSL tumour growth and that AZT, which was the only anti-neoplastic agent, was ineffective against lymphoma cell lines [1]. This finding is concordant to different highly toxic treatment experiences both in HIV-positive and HIV-negative PCNSL patients [4, 7, 8, 16].

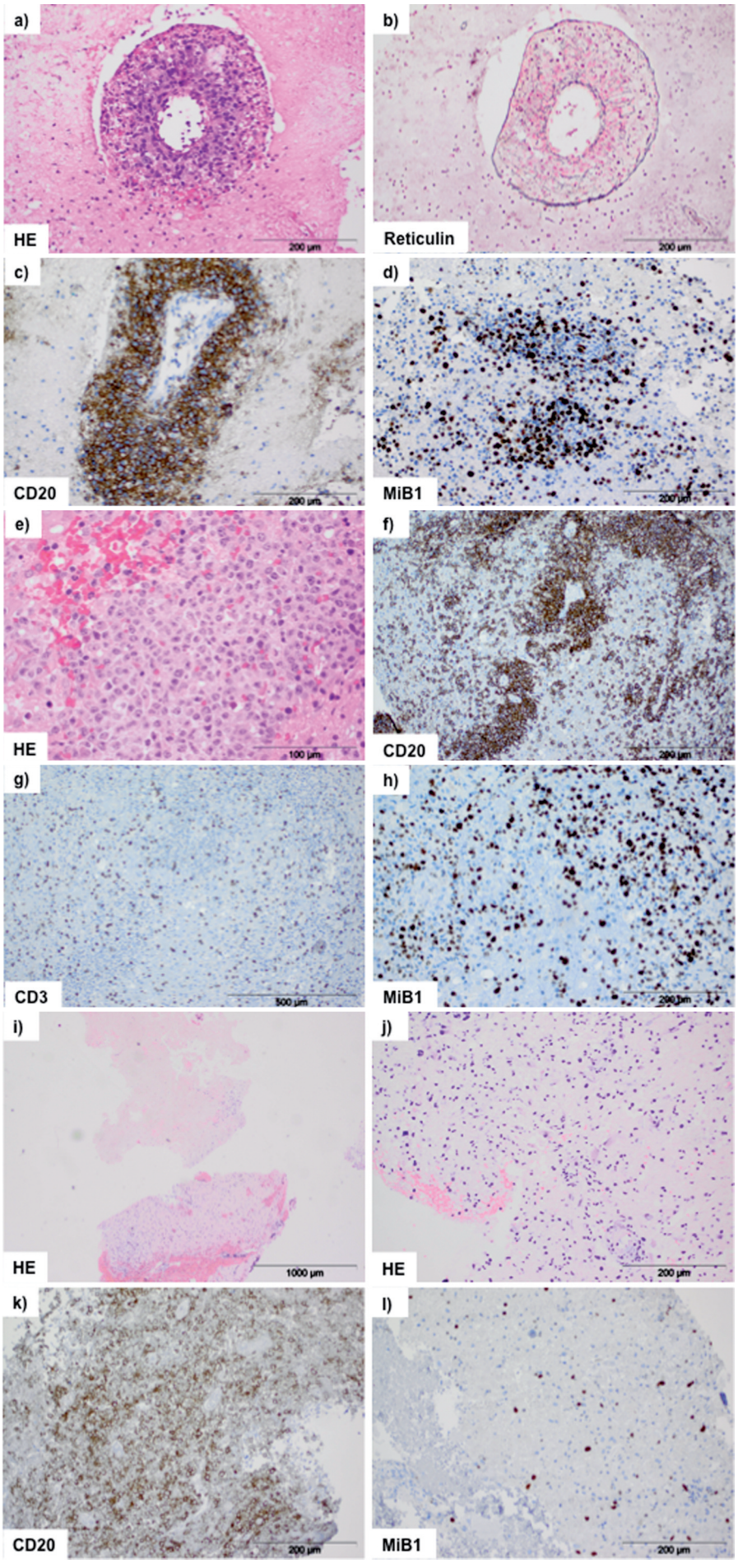
HAART was effective in immune reconstitution, but patient 2 did not take it regularly from the time of radiation therapy due to poor adherence.

Replacing ganciclovir by foscarnet during the induction phase helped to avoid the hematological toxicity of ganciclovir. Both agents as well as cidofovir are effective against EBV [25, 27]. Foscarnet has been shown to be effective in EBV-associated lymphoproliferations and is activated independently of viral encoded thymidine-kinase, which is an advantage over ganciclovir [28]. However, it was not effective in halting rapid tumor growth in these patients, which had already become independent from the original multifactorial pathogenesis of polyclonal EBV- and HIV-induced lymphoproliferation. Since the herpes-virus consensus PCR was negative in two of the patients' CSF prior to therapy, and not performed in one patient (histological diagnosis), EBV-viral load was not measured.

The reason for the reduced effectiveness of foscarnet compared to ganciclovir against EBV could be not be discerned, and it is unclear why Raez and Aboulafia elected to utilize ganciclovir.

Interleukin-2 was administered to induce an acceleration of immune response, and to decrease EBV-DNA [29]. Its clinical benefit in reducing opportunistic infections in HIV positive persons is not proven [30]. The observed rapid immune reconstitution of CD4 cells by combined antiretroviral and interleukin-2 administration in 2 patients was impressive, nevertheless it had no impact on tumour progression. Of note is that this did eventually contribute to stopping lymphoproliferation after radiation in patient 3, which is similar to four reported patients with longer lasting remissions by HAART and radiation [4].

Even though only lymphoproliferation had been diagnosed in patient 3, the lymphoproliferative polyclonal tumor with impressive necrotic tissue mass, which is pathognomonic for high grade lymphoma in the brain, was highly suspicious for PCNSL. Polyclonal lymphoproliferation as a pre-lymphoma stage could not be completely ruled out.



Patient 2
a), b) Diffuse large B-cell lymphoma within the central nervous tissue penetrating a blood vessel. c) The large tumor cells express the B-cell marker CD20 and reveal a high proliverative activity d).

Patient 1
e) In a further case H&E stained section shows a diffuse large B-cell lymphoma. Nearly all of the lymphoma cells show prominent central nucleoli. f) The tumor cells are reactive with antibodies against CD20. g) The mature T-cell react with antibodies against CD3. h) The proliferation marker MiB1 (Ki67) labels more than 50% of the tumor cells.

Patient 3
i, j) The H&E stained sections reveal necrotic cns tissue with reactive astrocytes, macrophages and inflammatory cells. k) With antibodies against CD20 some blastic B-cells where detectable. l) The proliferation marker Mib1 labels only some inflammatory cells.

Additionally, patient 3 was the only patient with a relatively stable immune status and without previous AIDS-defining illnesses at the time of diagnosis. Herpes-consensus PCR in his CSF was negative with EBV-positivity in histology, corresponding to a latent infection pattern without active EBV-replication.

Ritonavir has been reported to have antiangiogenic and radiation sensitizing effects in a mouse carcinoma model [31], and could eventually have had an influence on response, but only in this patient. However, after responding to radiation he continued HAART with long-term antiviral EBV therapy and was clinically stable over the following years.

HAART plus whole brain radiation appears to be the mainstay of treatment for HIV-associated PCNSL-patients with highly impaired immune and performance status.

In selected cases of HIV-positive PCNSL patients with sufficient performance status, systemic chemotherapy should be considered [16,32]. HAART and systemic chemotherapy, possibly even in patients with impaired immune status, can be considered in an attempt to induce immune reconstitution and thus improving both neurological and overall clinical status.

Combination chemo-radiotherapies in immunocompetent patients (most of them with intrathecal MTX and/or cytarabine, systemic methotrexate, procarbazine, vincristine, thiotepa, teniposide or carmustine) cause high rates of hematologic toxicity, treatment-related deaths in up to 10%, infection rates up to 19% and leukoencephalopathy rates of up to 30% (without radiation 3%). The median survival ranged from 32 to 55 months [7-9].

Systemic rituximab alone does not generally seem to be beneficial, but may be so only in selected patients [9, 33]. In a small series with relapsed or progressive disease in HIV-negative persons, intrathecal rituximab was shown to be safe and partially effective [34-36] and therefore stands as a possible option.

Systemic methotrexate (MTX) alone, 3-8 g/m² and delayed radiotherapy are most frequently used in HIV-negative patients, and show median survival times of 22 to 47 months with low neurotoxicity rates. [7-9].

Select HIV patients are reported to benefit from high-dose MTX alone: seven out of 15 patients treated with 3g/m² intravenous MTX without HAART showed a complete response after six cycles, with two of 15 patients dying from septicaemia [32]. Only a few HIV-positive patients with PCNSL were treated with systemic MTX [4, 32].

In the pre-HAART era, combined radio-chemotherapy with procarbazine, lomustine and vincristine (PCV-3) for HIV-related PCNSL patients with more than 200 CD4-cells/µl, who had a good performance status and without history of opportunistic infection, showed a median survival of 13 months [16].

Autologous stem-cell rescue with high-dose chemotherapy protocols were given successfully in immunocompetent PCNSL patients under the age of 60 years and achieved median survival rates of up to 60 months [11, 12, 37]. HIV-positive patients were excluded from high-dose studies due to safety reasons.

Temozolomide plus systemic MTX/ prednisone in an elderly patient group showed overall survival rates of 36 months, but severe nephrotoxicity and hematological toxicity occurred in 20% and 13% respectively [38] which is too toxic for AIDS-patients. A promising schedule for the elderly that utilizes three cycles of rituximab, methotrexate, lomustine, and procarbacine (R-MCP) has been described. The regimen is without radiation, has an acceptable safety profile, and a 12-month overall and disease-free survival of 81% in 16 patients [14]. This treatment modality could eventually become an option for HIV-positive PCNSL patients, considering that the oldest patient was 83 years old and that a reduced performance status was not an exclusion criteria.

Salvage regimens have been performed with topotecan, PCV (procarbacine, lomustine, vincristine), antracyclines, high-dose cytarabine, etoposide, ifosfamide, thiotepa, temozolomide, temozolomide/rituximab, radiotherapy and surgery [7, 8, 24, 39]. It remains unclear which of these can be considered in HIV-positive patients.

Conclusion

IL-2, HAART, AZT-high-dose and foscarnet were safe, but ineffective when used as the only therapy for HIV-associated PCNSL based on our experience with these 3 patients. A review of results in the medical literature is also inconsistent. The numbers of patients treated with similar regimens have been too few to allow any final conclusion. The deterioration of the overall clinical status in 2 out of 3 patients was rapid, and corresponded to the frequently encountered clinical course of newly diagnosed HIV-associated PCNSL patients, who often have co morbidities. Nevertheless, in select patients with advanced disease and without a systemic chemotherapeutic option, this type of regimen could be considered.

Raez and Aboulafia et al reported similar cases to the 3 patients that we have described. A favourable clinical course may more likely occur in select HIV infected patients with good performance status. Two of the 3 patients had severe co morbidities (TBC, Kaposi-sarcoma, cryptococcosis, psychosis), so chemotherapy was not a reasonable option. Therefore, this regimen was considered to be potentially beneficial. In the future, patients within clinical studies who have adequate performance status could qualify for more intensive systemic chemotherapy options combined with HAART to avoid late leukencephalopathy caused by radiation. It remains uncertain if interleukin-2, AZT high-dose and / or foscarnet can be added or be given sequentially with chemotherapy, especially in severe compromised patients at the beginning of therapy. Despite a substantial and sustained increase in the CD4-count, as compared with antiretroviral therapy alone, interleukin-2 plus antiretroviral therapy yielded no clinical benefit in HIV positive persons [30].

Regardless, most HIV-associated PCNSL patients are not cured with systemic chemotherapy [6]. If chemotherapy is utilized, multidisciplinary teams including specialists in haematology-oncology and infectious diseases will be needed to manage toxicities, drug-interactions, and specific infectious and other complications that can occur during and after therapy.

Clinicians should be diligent about detecting and treating CNS-lymphoma and other types of cancer in HIV positive patients, and should be encouraged by the improved prognosis due to HAART to treat CNS-lymphomas more intensively [18].

Finally, we emphasize the importance of performing clinical trials in HIV-positive patients with malignancies.

Conflict of interest statement: The author declares that she has no competing interests

REFERENCES

1. Raez L, Cabral L, Cai JP, et al. Treatment of AIDS-related primary central nervous system lymphoma with zidovudine, ganciclovir, and interleukin 2. AIDS Res Hum Retroviruses 1999; 15:713-719.
2. Cheung MC, Pantanowitz L, Dezube BJ. AIDS-related malignancies: emerging challenges in the era of highly active antiretroviral therapy. Oncologist 2005; 10: 412-426.
3. Wolf T, Brodt HR, Fichtlscherer S, et al. Changing incidence and prognostic factors of survival in AIDS-related non-Hodgkin's lymphoma in the era of highly active antiretroviral therapy (HAART). Leuk Lymphoma. 2005 Feb;46(2):207-15.
4. Hoffmann C, Tabrizian S, Wolf E, et al. Survival of AIDS patients with primary central nervous system lymphoma is dramatically improved by HAART-induced immune recovery. AIDS 2001; 15: 2119-2127.
5. Aboulafia DM, Ratner L, Miles SA, et al. Antiviral and immunomodulatory treatment for AIDS-related primary central nervous system lymphoma: AIDS Malignancies Consortium pilot study 019. Clin Lymphoma Myeloma 2006,6:399-402.
6 Kreisl T, Panageas K, Elkin E, et al. Treatment patterns and prognosis in patients with human immunodeficiency virus and primary central system lymphoma. Leuk Lymphoma 2008; 25:1-7
7. Batchelor T, Loeffler JS Primary CNS lymphoma. J Clin Oncol 2006; 24: 1281-1288.
8. Omuro, AMP, Abrey LE Chemotherapy for primary Central Nervous System Lymphoma Neurosurgical Focus 2006; 21(5): E12
09. DeAngelis LM, Iwamoto F. An Update on Primary Central Nervous System Lymphoma Hematology 2006; 1: 311-16
10. Gavrilovic IT, Hormigo A, Yahalom J, et al. Long-Term Follow-Up of High-Dose Methotrexate-Based Therapy With and Without Whole Brain Irradiation for Newly Diagnosed Primary CNS Lymphoma. J. Clin Oncol. 2006; 1(24): 4570-4
11. Illerhaus G, Marks R, Ihorst G, et al. High-Dose Chemotherapy With Autologous Stem-Cell Transplantation and Hyperfractioned Radiotherapy As First-Line Treatment of Primary CNS Lymphoma. J Clin Oncology, 2006; 24: 1-8
12. Soussain C, Suzan F, Hoang-Xuan K, et al. Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma J Clin Oncol 2001, 19(3): 742-749 (follow-up Soussain, 2008 JCO 26: 2512-18)
13. Cheng T, Forsyth P, Chaudhry A, et al. High-dose thiotepa, busulfan, cyclophosphamide and ASCT without whole-brain radiotherapy for poor prognosis primary CNS lymphoma Bone Marrow Transplantation 2003, 31: 679-685
14. Illerhaus G, Markert A, Feuerhake F, et al. Immuno-Chemotherapy with Rituximab, Methotrexate, CCNU and Procarbazine for the treatment of Primary CNS-Lymphoma in the Elderly Onkologie 2008; 31 (suppl 4)11
15. Skiest DJ, Crosby C Survival is prolonged by highly active antiretroviral therapy in AIDS patients with primary central nervous system lymphoma AIDS 2003;17(12): 1787-93
16. Chamberlain MC, Kormanik PA. AIDS-related central nervous system lymphomas. J Neurooncol, 1999; 43: 269-276.
17. Baumgartner JE, Rachlin JR, Beckstead JH, et al. Primary central nervous system lymphomas: natural history and response to radiation therapy in 55 patients with acquired immunodeficiency syndrome. J Neurosurg 1990,73: 206-211.
18. Diamond C, Taylor TH, Aboumrad T, et al. Changes in acquired immunodeficiency syndrome-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: incidence, presentation, treatment, and survival Cancer Jan 2006; 106(1): 128-35
19 Re A, Tucci A, Casari S, et al. Treating Lymphoma with Curative Intent in HIV Positive Patients after the Advent of HAART: A Comparative Analysis with the HIV Negative Population ASH Poster Board, December 2008; III-685, 3603
20 Aboulafia DM, Puswella AM. Case Report: Highly Active Antiretroviral Therapy as the Sole Treatment for AIDS-Related Primary Central Nervous System Lymphoma: A Case Report with Implications for Treatment AIDS Patient Care and STDs 2007, 21(12): 900-907
21 Chotmongkol, V, Pesee M AIDS-Related Primary Central Nervous System Lymphoma: Prolonged Remission Associated with Highly Active Antiretroviral Therapy J Med Assoc Thai 2002; 85: 634-637
22 McGowan JP, Shah S. Long-term remission of AIDS-related primary central nervous system lymphoma associated with highly active antiretroviral therapy AIDS 1998 12: 952-54
23 Corales R, Taege A, Rehm S, et al. Regression of AIDS-related CNS lymphoma with HAART XIII International AIDS Conference, Durban 2000 (abstract MoPpB1086)
24. Fischer L, Thiel E, Klasen HA, et al. Prospective trial on topotecan salvage therapy in primary CNS lymphoma. Ann Oncol 2006;17(7):1141-5.
25. Bossolasco S, Falk KI, Ponzoni M, et al. Ganciclovir is associated with low or undetectable Epstein-Barr virus DNA load in cerebrospinal fluid of patients with HIV-related primary central nervous system lymphoma. Clin Infect Dis 2006; 42: 21-25.
26. M. Hänel, F. Fiedler, C. Thorns. Anti-CD20 Monoclonal Antibody (Rituximab) and Cidofovir as Successful Treatment of an EBV-Associated Lymphoma with CNS Involvement. Onkologie 2001; 24(5): 491-494.

Gershburg E, Pagano JS. Epstein–Barr virus infections: prospects for treatment. J Antimicrobial Chemotherapy 2005; 56(2):277-281

28. Oertel SH, Riess H. Antiviral treatment of Epstein-Barr virus-associated lymphoproliferations. Recent Results Cancer Res 2002; 159: 89-95.
29. Burighel N, Ghezzi S, Nozza S, et al. Differential dynamics of Epstein-Barr virus in individuals infected with human immunodeficiency virus-1 receiving intermittent interleukin-2 and antiretroviral therapy. Haematologica 2006; 91: 244-247.
30 Abrams D, Levy Y, Tambussi G et al. Interleukin-2 Therapy in Patients with HIV Infection N Engl J Med 2009;361:1548-59.
31 Maggiorella L; Wen B; Frascogna V; et al. Combined radiation sensitizing nd anti-angiogenic effects of ionizing radiation and the protease inhibitor ritonavir in a head and neck carcinoma model Anticancer Res. 2005; 25(6B): 4357-62.

32. Jacomet C, Girard PM, Lebrette MG, et al. Intravenous methotrexate for primary central nervous system non-Hodgkin´s lymphoma in AIDS. AIDS 1997; 11: 1725-30
33. Herrlinger U, Korfel A, Hebart H, et al. Meeting Report: Primary Central Nervous System Lymphoma: Standards Of Care And Future Perspectives. Onkologie 2005; 28-2: 109-111 Congress Report
34. Antonini G, Cox MC, Montefusco E, et al. Intrathecal CD-20 antibody an effective and safe treatment for leptomeningeal lymphoma J Neuro-Oncology 2007; 81(2): 197-199
35 Pels H, Schulz H, Schlegel U, et al. Treatment of CNS Lymphoma with the Anti-CD20 Antibody Rituximab: Experience with Two Cases and Review of the Literature Onkologie 2003; 26: 351-354
36 Rubenstein JL, Fridlyand J, Abrey L, et al. Phase I Study of Intraventricular Administration of Rituximab in Patients With Recurrent CNS and Intraocular Lymphoma J Clin Oncology 2007; 25(11): 1350-1356
37. Abrey LE, Craig H. Moskowitz WPM, et al. Intensive Methotrexate and Cytarabine Followed by High-Dose Chemotherapy With Autologous Stem-Cell Rescue in Patients With Newly Diagnosed Primary CNS Lymphoma: An Intent-to-Treat Analysis. J Clin Oncology Nov 2003; 21(22): 4151-4156
38. Omuro AMP, Taillandier L, Chinot O, et al. Temozolomide and methotrexate for primary central nervous system lymphoma in the elderly J Neuro-Oncology 2007; 85(2): 207-211
39. Sakamoto M, Oya N, Mizowaki T, et al. Initial experiences of palliative stereotactic radiosurgery for recurrent brain lymphomas. J Neurooncol 2006,77:53-58.
40 Newell ME, Hoy JF, Cooper SG et al. Human immunodeficiency virus–related primary central nervous system lymphoma. Factors influencing survival in 111 patients Cancer 2004; 100 (12): 2627–2636

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