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Long-term follow-up of high-dose chemotherapy with autologous stem-cell transplantation and response-adapted whole-brain radiotherapy for newly diagnosed primary CNS lymphoma: results of the multicenter Ostdeutsche Studiengruppe Hämatologie und Onkologie OSHO-53 phase II study

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Background: We previously reported the results of a phase II study for patients with newly diagnosed primary central nervous system lymphoma treated with autologous peripheral blood stem-cell transplantation (aPBSCT) and response-adapted whole-brain radiotherapy (WBRT). Now, we update the initial results.

Patients and methods: From 1999 to 2004, 23 patients received high-dose methotrexate. In case of at least partial remission, high-dose busulfan/thiotepa (HD-BuTT) followed by aPBSCT was carried out. Patients refractory to induction or without complete remission after HD-BuTT received WBRT. Eight patients still alive in 2011 were contacted and Mini-Mental State Examination (MMSE) and the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire (QLQ)-C30 were carried out.

Results: Of eight patients still alive, median follow-up is 116.9 months. Only one of nine irradiated patients is still alive with a severe neurologic deficit. In seven of eight patients treated with HD-BuTT, health condition and quality of life are excellent. MMSE and QLQ-C30 showed remarkably good results in patients who did not receive WBRT. All of them have a Karnofsky score of 90%–100%.

Conclusions: Follow-up shows an overall survival of 35%. In six of seven patients where WBRT could be avoided, no long-term neurotoxicity has been observed and all patients have an excellent quality of life.

Key words: autologous stem-cell transplantation, long-term follow-up, methotrexate, neurotoxicity, primary CNS lymphoma

introduction

Primary central nervous system lymphoma (pCNSL) is a rare malignant non-Hodgkin's lymphoma of B-cell origin. Whole-brain radiotherapy (WBRT) as the sole treatment modality is associated with an overall response rate of up to 90% but a very high relapse rate and a median overall survival (OS) of 1 year. In addition, WBRT is associated with an increased likelihood of treatment-related toxicity, especially in patients >60 years [1]. To improve these results, WBRT has been combined with high-dose methotrexate (HD-MTX), the most effective chemotherapeutic agent for pCNSL. Combination of methotrexate (MTX) and WBRT increased the 2-year survival

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Table 1. Patient characteristics including the results of quality-of-life measurement

Age/sex	HD-BuTT	WBRT	Neurotoxicity	LFU/status/CoD	MMSE	QLQ-C30	Remarks
67/male	+	−	−	47 months/CR, dead/pneumonia	–	–	
58/male	+	+	+	27 months/CR, dead/neurotoxicity	–	–	
48/female	−	+	+	19 months/PD, dead/relapse	–	–	
68/female	+	−	+	12 months/SU, dead/relapse	–	–	
56/male	−	−	−	Day 26 after MTX/NC, dead/PE	–	–	
63/male	+	+	+	6 months/PR, dead/neurotoxicity	–	–	
66/male	−	+	+	20 months/CR, dead/neurotoxicity	–	–	
61/female	+	−	−	3 months/CR, dead/pneumonia	–	–	
63/female	−	+	+	19 months/CR, dead/relapse	–	–	
55/male	−	+	−	3 months/SU, dead/cardiac/PE	–	–	
18/female	+	−	+	10 months/CR, dead/pneumonia	–	–	
52/male	+	−	−	1 month/SU, dead/septic MOF	–	–	
51/female	+	−	−	Day 6/SU, dead/septic MOF	–	–	
52/male	−	+	−	58 months/CR, dead, relapse	–	–	
53/female	+	+	+	38 months/CR, dead, relapse	–	–	
42/female	+	−	−	141 months/CR, alive	n.e.	n.e.	Gall-bladder carcinoma
51/female	+	−	−	123 months/relapse → CR, alive	24	33/28	CR after relapse, follow-up 5 months
48/male	+	−	−	123 months/CR, alive	30	35/28	
40/male	+	−	−	118 months/CR, alive	29	28/28	
60/male	+	−	−	4 months after HDC testicular relapse, salvage therapy/115 months/CR, alive	28	40/28	
56/male	+	−	−	79 months/CR, alive	27	40/28	
54/female	−	+	+	88 months/CR, alive	20	60/28	Severe neurological deficit
69/female	+	−	+	93 months/CR, neurological deficit, alive	17[a]	41[a]/28	Lost to follow-up, last follow-up November 2009

[a]Data from November 2009.

CoD, cause of death; CR, complete remission; HD-BuTT, high-dose busulfan/thiotepa; HDC, high-dose chemotherapy; LFU, length/status of last follow-up; MMSE, Mini-Mental State Examination; MOF, multiorgan failure including ventilation; MTX, methotrexate; NC, no change; n.e., not evaluable; neurotoxicity, clinically relevant neurotoxicity; PD, progressive disease; PE, pulmonary embolism; PR, partial remission; QLQ, quality-of-life questionnaire; SU, remission status unknown; WBRT, whole-brain radiotherapy.

from 43% to 73% [2]; however, the combination of MTX and WBRT is associated with a high risk of delayed neurotoxicity, primarily in elderly patients [3]. To avoid neurological deficits, we initiated a phase II study [Ostdeutsche Studiengruppe Hämatologie und Onkologie (OSHO)-53 study] for patients with newly diagnosed pCNSL to be treated with high-dose busulfan/thiotepa (HD-BuTT) followed by autologous peripheral blood stem-cell transplantation (aPBSCT) and response-adapted WBRT after induction therapy with HD-MTX. The results of this study were published in 2006 [4]. Here, we give a long-term follow-up after >10 years after study initiation.

patients and methods

Twenty-three immunocompetent patients with histological diagnosis of pCNSL received HD-MTX. Patients that achieved a complete remission (CR) or partial remission received HD-BuTT with aPBSCT. Patients in CR after high-dose chemotherapy received no further treatment, all others were treated with whole-brain irradiation. Patient characteristics and the details of the study protocol have been reported [4]. All living patients have been contacted now to evaluate OS and Mini-Mental State Examination (MMSE) to assess a possible cognitive deficiency. Maximum score for no mental restriction is 30 points. A quality-of-life questionnaire (QLQ)-C30 was used to assess quality of life. Twenty-eight points indicate the best possible quality of life. The number of points is inversely correlated with the quality of life.

results

In our initial publication in 2006, we showed the results after a follow-up range of 1–69 months [4]. Median follow-up now is 26 months (range 1.4–141). Eight of the 23 patients enrolled in this study are still alive, while 15 patients died. Causes of death were multiorgan failure (two patients), neurological toxicity (three patients after WBRT), pneumonia (three patients; 3, 10, and 47 months after diagnosis), pulmonary embolism (two patients; 3 and 26 months after start of therapy) (Table 1). Fatal relapses occurred in five patients. All relapses emerged later than 12 months from diagnosis (12, 19, 19, 38, and 58 months). One testicular relapse occurred 4 months after aPBSCT. The patient received chemotherapy (R-CHOP) and is alive and in CR, 115 months after diagnosis of pCNSL. One additional relapse occurred 103 months after therapy; rescue

therapy (carmustine/thiotepa followed by aPBSCT) has led to a CR lasting now for 5 months. In another patient, a carcinoma of the gall-bladder was detected and she is still receiving chemotherapy. The remaining six patients are in CR. The OS and time to treatment failure, defined as relapse or death due to pCNSL or treatment-related causes of all patients, are shown in Figure 1. The results from the questionnaires (MMSE and QLQ-C30) are shown in Table 1. Except for one female patient, all patients who did not receive WBRT revealed excellent results upon examination, i.e. between 24 and 30 points in the MMSE (median 28 points) and between 33 and 40 points (median 35 points) in the QLQ-C30 with no restriction reported in their daily life due to neurological deficits. A 69-year-old female patient with neurological deficits despite no irradiation is the oldest patient in this trial and actually lost to follow-up. In November 2009, we were able to carry out the tests and she showed MMSE only of 17 points but 41 points in QLQ-C30. She needed no help to dress up, was able to wash herself, and could independently go for a walk. She was living with her daughter and both were quite satisfied. The patient who got WBRT reached only 20 points in the MMSE. Most of the day, she was sitting in a chair due to severe neurological deficit. She needed help to dress up, was not able to wash herself, and was visited two times a day by a nurse. QLQ-C30 of this patient shows 60 points, which documents restricted quality of life, but the patient told us to be satisfied with her health and quality of life. Upon univariate analysis, we found a correlation of the length of the interval between initial diagnosis and initiation of HD-MTX therapy with outcome. If the period exceeded 20 days, there was a significantly worse OS (log-rank test, chi-square test, $P = 0.046$) (Figure 2). No significant impact of age (>/< 60 years), gender, initial Karnofsky score (>/< 70%), initial lactate dehydrogenase level of serum, and time between the first and the second HD-MTX cycle was seen.

discussion

In this article, we report a long-term follow-up of patients with pCNSL having been treated in the OSHO-53 study. When we started this study in 1999, the main question we wanted to answer was whether patients with pCNSL receiving two cycles of HD-MTX followed by HD-BuTT with aPBSCT have a survival rate comparable with studies using chemotherapy plus WBRT regularly. In order to achieve a high tumoricidal impact, we have chosen a dose-dense protocol including two cycles of HD-MTX and HD-BuTT with aPBSCT within 28 days. As shown by univariate analysis (Figure 2), it is important to treat patients with pCNSL as soon as possible after diagnosis. We hoped to show that by omitting WBRT, less neurotoxicity can be observed and a better quality of life later on can be achieved. Analyzing our data 10 years after initiating the study, we see an OS of 35%, which is not inferior to other studies using a combination of chemotherapy and WBRT. Blay et al. [3] shows a 5-year survival of 19%, Poortmans et al. [5] 58% OS after 3 years, and DeAngelis et al. [6] 30% after 5 years. In addition, Thiel et al. [7] reported recently no significant difference in OS when WBRT was omitted from first-line chemotherapy in patients with newly diagnosed pCNSL. In this study, a HD-MTX-based chemotherapy was used without aPBSCT. In order to investigate the long-term neurotoxicity in our study protocol, we analyzed the MMSE and QLQ-C30. The patient that was treated with WBRT because of a lack of response to HD-MTX shows severe neurological deficits. Her daily activity is markedly reduced as described above. Results from MMSE and QLQ-C30 show very bad results. Of the remaining seven patients that were treated with HD-BuTT, questionnaires could only be completed by five patients. The patient with the recently diagnosed gall-bladder carcinoma denied to participate. Another patient has moved to an unknown place, but in November 2009, she filled out the questionnaires with a bad MMSE but a good QLQ-C30 result.

As described in other studies, late relapses are not uncommon [5, 8, 9]. We saw the latest relapse after >100 months, which underlines the importance of regular and long-lasting follow-up, since a promising salvage therapy is available [10–14].

One systemic relapse in the testis occurred and could be successfully managed with R-CHOP chemoimmunotherapy.

In summary, the results of this study show that HD-MTX with HD-BuTT followed by aPBSCT results in long-term disease control in about one-third of the patients. Most of

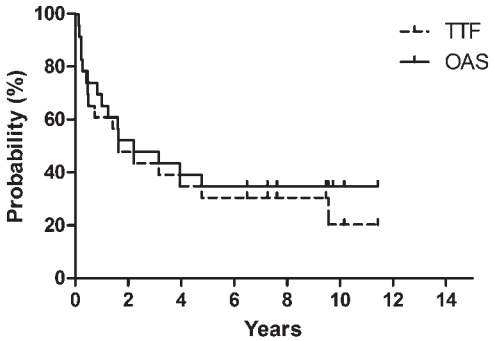

Figure 1. Overall survival (OS) and time to treatment failure (TTF) of all 23 patients who had been enrolled in the study. Treatment failure was defined as relapse or death due to primary central nervous system lymphoma or treatment-related reasons.

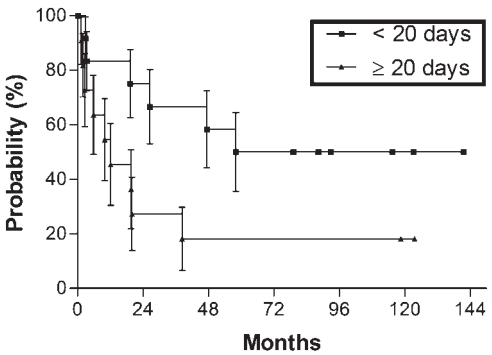

Figure 2. Overall survival depending on the time interval between initial diagnosis and start of therapy with high-dose methotrexate. Log-rank test, $P = 0.046$, standard error of the mean, SEM.

them show no compromising cognitive functions and have an excellent quality of life. These long-term results support ongoing treatment efforts aiming to increase the tumor-eradicating potential of primary therapy, to minimize early mortality, and to avoid neurotoxicity due to WBRT. Adding rituximab, cytarabine, and thiotepa to HD-MTX, the ongoing randomized trial NCT01011920, initiated by A. Ferreri, will help to establish a more effective therapy strategy before high-dose chemotherapy and aPBSCT.

disclosure

The authors declare no conflict of interest.

references

1. Nelson DF, Martz KL, Bonner H et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. Int J Radiat Oncol Biol Phys 1992; 23: 9–17.
2. Ferreri AJ, Abrey LE, Blay JY et al. Summary statement on primary central nervous system lymphomas from the Eighth International Conference on Malignant Lymphoma, Lugano, Switzerland, June 12 to 15, 2002. J Clin Oncol 2003; 21: 2407–2414.
3. Blay JY, Conroy T, Chevreau C et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. J Clin Oncol 1998; 16: 864–871.
4. Montemurro M, Kiefer T, Schuler F et al. Primary central nervous system lymphoma treated with high-dose methotrexate, high-dose busulfan/thiotepa, autologous stem-cell transplantation and response-adapted whole-brain radiotherapy: results of the multicenter Ostdeutsche Studiengruppe Hamato-Onkologie OSHO-53 phase II study. Ann Oncol 2007; 18: 665–671.
5. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H et al. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. J Clin Oncol 2003; 21: 4483–4488.
6. DeAngelis LM, Seiferheld W, Schold SC et al. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. J Clin Oncol 2002; 20: 4643–4648.
7. Thiel E, Korfel A, Martus P et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. Lancet Oncol 2010; 11: 1036–1047.
8. Omuro A, Taillandier L, Chinot O et al. Primary CNS lymphoma in patients younger than 60: can whole-brain radiotherapy be deferred?. J Neurooncol 2010; 104(1): 323–330.
9. Illerhaus G, Marks R, Muller F et al. High-dose methotrexate combined with procarbazine and CCNU for primary CNS lymphoma in the elderly: results of a prospective pilot and phase II study. Ann Oncol 2009; 20: 319–325.
10. Enting RH, Demopoulos A, DeAngelis LM et al. Salvage therapy for primary CNS lymphoma with a combination of rituximab and temozolomide. Neurology 2004; 63: 901–903.
11. Herrlinger U, Brugger W, Bamberg M et al. PCV salvage chemotherapy for recurrent primary CNS lymphoma. Neurology 2000; 54: 1707–1708.
12. Nguyen PL, Chakravarti A, Finkelstein DM et al. Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma. J Clin Oncol 2005; 23: 1507–1513.
13. Reni M, Mason W, Zaja F et al. Salvage chemotherapy with temozolomide in primary CNS lymphomas: preliminary results of a phase II trial. Eur J Cancer 2004; 40: 1682–1688.
14. Voloschin AD, Betensky R, Wen PY et al. Topotecan as salvage therapy for relapsed or refractory primary central nervous system lymphoma. J Neurooncol 2008; 86: 211–215.