erratum

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Prognosis after high-dose chemotherapy followed by autologous stem-cell transplantation as first-line treatment in primary CNS lymphoma—a long-term follow-up study

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In the original version of this paper in the issue, an error occurred whereby several instances of the number '1' had dropped out of the PDF. The corrected sections read as below.

The Publisher apologizes for the error.

results

study I

After a median follow-up of 140 months, 10/30 patients are still alive. Median survival was reached after 104 months. Five- and 10-year OS estimates were 67% [95% confidence interval (CI) 52% to –86%] and 42% (95% CI 28% to –65%) (Figure 1). EFS estimates after 5 and 10 years were 67% (95% CI 52% to 86%) and 40% (95% CI 25% to 62%), respectively. In the per-protocol analysis, median survival was reached after 122 months. Five- and 10-year OS probability was 83% (95% CI 69%–100%) and 56% (95% CI 39%–81%) and EFS probability after 5 and 10 years was 83% (95% CI 69%–100%) and 52% (95% CI 35%–77%), respectively.

study II

After a median follow-up of 72 months, 9/13 patients are still alive. The median survival was not reached at the time of last follow-up. Both 2- and 5-year OS estimates were 77% (95% CI 57%–100%) (Figure 2). Two- and 5-year EFS estimates were 77% (95% CI 57%–100%) and 70% (95% CI 48%–100%), respectively. In the per-protocol population, 8/11 patients are still alive. Both 2- and 5-year OS estimates were 82% (95% CI 62%–100%); 2- and 5-year EFS estimates were 82% (95% CI 62%–100%) and 73% (95% CI 51%–100%), respectively.

pooled analysis of the whole cohort

In the entire intention-to-treat group ($N = 43$), after a follow-up of 110 months, the median OS was reached at 104 months. Two- and 5-year OS was 81% (95% CI 71%–94%) and 70% (95% CI 57%–85%), respectively (supplemental Figure S2, available at *Annals of Oncology* online). Two- and 5-year EFS was 81% (95% CI 70%–94%) and 67% (95% CI 55%–83%), respectively. In the per-protocol analysis, the median OS was reached after 122 and median EFS after 104 months. The estimated 5-year OS and EFS was 82% (95% CI 71%–96%) and 79% (95% CI 67%–94%), respectively. In multivariate Cox regression analysis, neither age [hazard ratio (HR) = 1.55, 95% CI 0.95–2.55, $P = 0.08$] nor KPS (HR = 1.04, 95% CI 0.83–1.30, $P = 0.7284$) had a significant impact on survival. However, the HR and the rather small P value for the coefficient age suggest a trend that with higher age the survival probability decreases.

relapse from CR

Of those patients achieving CR, in study I, after the last follow-up, additional four patients relapsed (all together 10/25; 40%, 95% CI 22%–61%). Of those, only one was successfully salvaged with a second HCT–ASCT and is ongoing CR. Regarding the per-protocol population from study I, the overall relapse rate was lower (7/22; 32%, 95% CI 0.15%–0.55%). In study II, previously one patient was reported to suffer from relapse (CNS and systemic) after achieving CR. Now, one additional female patient relapsed (altogether 2/9; 22%, 95%, CI 4%–60%), but she was successfully salvaged by immuno-polychemotherapy (rituximab, MTX, lomustine, and procarbazine).

In the entire cohort, 12 of 34 patients who achieved CR relapsed (35%; 95% CI 20%–54%) and of those, six relapsed 5 years after diagnosis (18%; 95% CI 7%–35%). The relapse rate in the per-protocol population was lower, here, only 9 of 30 patients who achieved CR relapsed (30%; 95% CI 15%–50%). Figure 3 illustrates the cumulative incidence function of the probability to die of PCNSL with other causes of death as competing risk in the per-protocol population. The estimated risk of death due to PCNSL after 5 years was 15% compared with 3% of death due to other cause.

long-term survivors (over 5 years)

The characteristics of 28 patients who survived 5 years and longer after diagnosis are summarized in supplemental Table S1 (available at *Annals of Oncology* online). Of those, only two who experienced a relapse were successfully salvaged and are still alive (patient 20 and 23). One female patient (44 years of age) developed late onset neurotoxicity during follow-up. She was irradiated

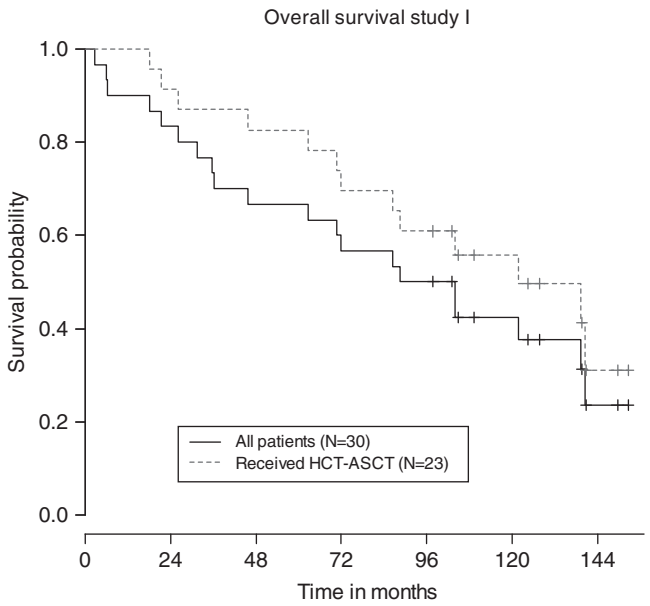

Figure 1. Overall survival study I ($N = 30$). HCT–ASCT, high-dose chemotherapy followed by autologous stem-cell transplantation.

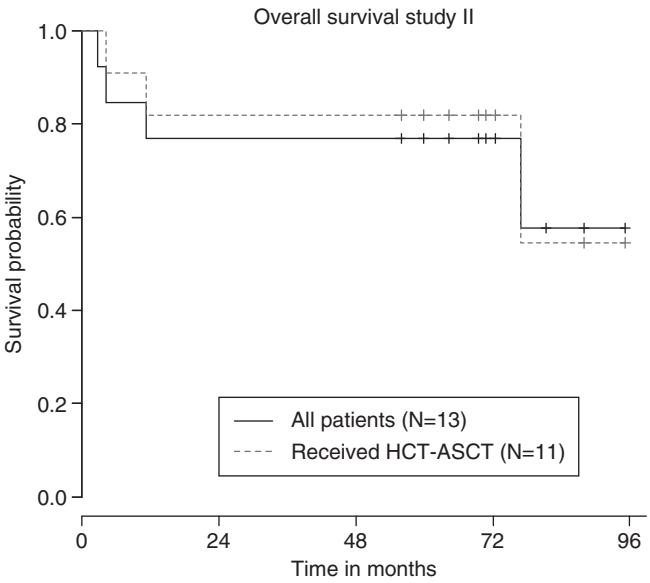

Figure 2. Overall survival study II ($N = 13$). HCT–ASCT, high-dose chemotherapy followed by autologous stem-cell transplantation.

because of only obtaining partial remission after HCT–ASCT (patient 25). One patient died due to severe neurotoxicity (patient 2). Altogether, six patients relapsed after > 5 years. During first-line treatment, five of these six patients received HCT–ASCT according to study protocol (one refused WBRT after HCT–ASCT, patient 20) and one patient (patient 8) was only irradiated due to renal failure developed after the second HD-MTX application (stable disease at that time, CR after WBRT). In these five patients who received HCT–ASCT, first CR was observed (i) during induction treatment with HD-MTX ($N = 2$, patients 5 and 20), (ii) after HCT–ASCT ($N = 1$, patient 10), and (iii) after WBRT ($N = 2$, patients 2 and 3). There were no apparent differences compared with all other patients regarding histology.

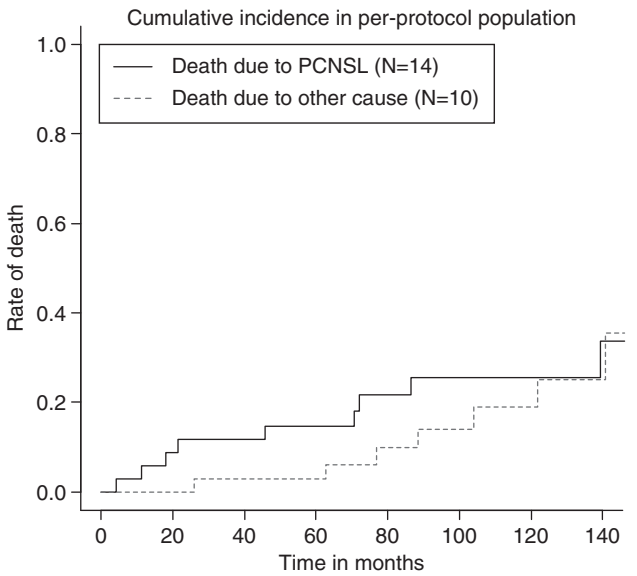

Figure 3. Cumulative incidence rates of death due to primary central nervous system lymphoma with death due to other cause as competing risk in the per-protocol population ($N = 34$).

WBRT versus no-WBRT

We dichotomized our cohort in patients who received WBRT ($N = 30$, for consolidation $N = 26$, for salvage $N = 4$) and those who did not ($N = 13$) to describe the association between WBRT and clinical apparent neurotoxicity. Of those eight (19%) patients who developed neurotoxicity during the entire follow-up, all were irradiated [$N = 7$ (as planned in study I), $N = 1$ (from study II due to partial response (PR) after HCT–ASCT)]. None of the patients who solely underwent HCT–ASCT developed neurotoxicity. Furthermore, regarding efficacy, patients who received HCT–ASCT without consolidating WBRT ($N = 10$; two from study I, eight from study II) achieved a response rate of 100% (nine CR, one PR); 2- and 5-year OS rates were 80% (95% CI 59 to 100) and 70% (95% CI 47 to 100), respectively.

discussion

The present study provides long-term data of patients with newly diagnosed PCNSL who were treated according to our previously published HCT–ASCT containing protocols [13, 14]. So far, eight studies (including ours) reported outcome after HCT–ASCT containing regimens for first-line treatment in PCNSL patients [13, 14, 17–22] (supplemental Table S2, available at *Annals of Oncology* online). Median follow-up ranged between 15 and 63 months (number of patients, 6–30) and conditioning regimens as well as survival rates varied strongly among the studies. To our best knowledge, no other study has yet reported comparable long-term data as reported in the present analysis regarding the treatment approach using HCT–ASCT in newly diagnosed PCNSL and for the population up to 65 years, no superior outcome data were published.

According to a recent review, only few studies reached a median OS of 60 months or longer [1]. Recently published long-term follow-up data of the 'Bonn Protocol' (median

follow-up 100 months for surviving patients) show a median OS of 54 months for the whole study population, but the median OS for patients younger than 60 years ($N = 30$) has not been reached yet [23]. Another recent publication reports a median OS of 33 months after a median follow-up of 83 months; however, this prospective multicenter trial was stopped due to toxicity and slow accrual [24]. These examples reflect the still existing heterogeneity of outcomes which may be caused by several differences regarding treatment protocols, study design (single center versus multicenter), type of analysis (retrospective versus prospective), age limit but also baseline risk factors. In fact, besides age and KPS, which are both wellestablished clinical prognostic factors, several other factors such as serological markers but also pharmacokinetic parameters of MTX have been proposed to potentially identify risk groups [25–27], but most of these findings still lack external validation from larger cohorts. Another cause of the observed heterogeneity is of course random variability due to the relatively small numbers of patients. However, with all these limitations, the now achieved median OS of 104 months for patients up to 65 years in our cohort is encouraging. Unfortunately, late relapses still occurred and one additionally needs to consider the fact that patients regarded eligible for this aggressive treatment approach are still a selected subpopulation and do not represent the majority of PCNSL patients. Especially elderly patients above 65 years who comprise about 50% of PCNSL patients are mostly not eligible for HCT–ASCT and are referred to other treatment regimens [28], but thorough clinical baseline risk evaluation beyond age should be done and if elderly patients have a good performance status, they maybe also considered as candidates for HCT–ASCT.

It is known that substantial proportions of patients who achieve CR experience relapse mostly during the first 2 years after diagnosis [9]. Nayak et al. recently published comprehensive data from 378 PCNSL patients; of those, 268 achieved a CR and 230 of them relapsed (86%; 95% CI 81%–90%). With regard to the narrow CI, these data give a rather good estimate of the true relapse rate. The authors further report that relapses after 5 years in CR were rare but did occur in 3.7% [8]. Compared with the overall relapse rate, our data compare favorably well with the data reported by Nayak et al.; however, because recurrence occurred later, our rate of patients who relapsed after 5 years is higher (18%) and only one of our patients with such late relapse has successfully been salvaged with a second HCT–ASCT containing a busulfan conditioning regimen and is in ongoing CR [29]. It seems that even after an upfront aggressive treatment approach, such as HCT–ASCT, some clonal malignant cells persist within the organism and patients are still at risk for relapse even after 5 years and longer.

Although WBRT is effective in disease control, the risk for short- and long-term neurotoxicity as well as the low positive impact on OS has recently questioned its role in first-line therapy [5, 7], but data from the recent randomized non- inferiority trial need to be taken with care since it was under powered and the induction treatment mainly based on HDMTX monotherapy [7, 30]. In fact, dose-reduced WBRT (23.4 Gy) is reported to be not associated with neurocognitive decline but still excellent disease control for patients achieving CR after treatment according to the R-MPV regimen (rituximab, MTX, procarbazine, and vincristine) [31]. On the other hand, Bessel et al. [32] reported compromised disease control after reducing the WRBT dose from 45 to 30.6 Gy, but the comparison between these two cohorts is difficult since induction polychemotherapies varied. As previously reported, the rate of clinical apparent neurotoxicity in our first study was relatively high (16.7%) in patients receiving both, HCT–ASCT and hyperfractionated WBRT [13]. Unfortunately, the rate in patients from study I increased during long-term follow-up to 23.3%. One limitation of this analysis was the lack of prospective standardized testing for neurocognition at baseline and during follow-up, thus the reported risk for neurotoxicity might even be underestimated. However, in study II, in order to decrease the risk of neurotoxicity without lacking efficacy, we improved the protocol by adding another cycle of cytarabine/thiotepa before stem-cell harvest and by doubling the thiotepa cumulative dose (4×5 mg/kg) within the conditioning regimen. In contrast to the earlier study, all patients were supposed to proceed to HCT–ASCT irrespective of their response to HD-MTX. The OS of study II was similar to the previous study with obligatory WBRT and we observed only one female patient developing severe neurotoxicity after being irradiated because of PR after chemotherapy. Of note, the 3-year OS prognosis (82%) of the per-protocol analysis of study II is comparable to that estimated for patients suffering from systemic aggressive diffuse large cell b-cell lymphoma who were at low to intermediate risk (3-year OS 81%) and treated in the rituximab era [33]. Granted treatment-related mortality (TRM) is an issue to be considered when HCT–ASCT is applied in first-line therapy, but in both studies, we observed no deaths in association with HCT–ASCT. Additionally, following a systematic review of HCT–ASCT in systemic lymphoma, estimated TRM of 6% was not increased compared with standard chemotherapy [34]. Therefore, basing on our data, not only with regard to the lower risk of neurotoxicity but also the systemic approach of eliminating residual lymphoma cells in all possible chemotherapy sanctuaries including the cerebrospinal fluid, HCT–ASCT could be an effective alternative to WBRT as consolidation therapy. Nevertheless, results from our national multicenter trial that has recently finished recruiting ($N = 81$) need to be awaited. In this trial, rituximab was added to the induction treatment and WBRT was restricted to those who did not achieve CR after HCT–ASCT (NCT00647049) in accordance to study II.

Sequential HD-MTX-based chemotherapy followed by carmustine/thiotepa-containing HCT–ASCT is a promising treatment option leading to remarkable median survival rates of almost 9 years in eligible patients. The role of HCT–ASCT compared with WBRT as consolidation in first-line therapy is currently under investigation in an international randomized trial (NCT01011920), which also evaluates three different combinations of induction treatments for efficacy and safety. With the improvement of chemotherapy protocols for PCNSL, another question that should be addressed in the future is whether HCT–ASCT is really superior to a potent immuno-polychemotherapy combination or may be deferred and saved as an option in case of relapse.

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