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ASHAP – an effective salvage therapy for recurrent and refractory malignant lymphomas

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Abstract *Background:* This study was performed to examine the efficacy and toxicity of the combination of adriamycin (ADR), methylprednisolone (solumedrol), cytarabine (Ara-C), and cisplatin (CDDP) in patients with recurrent and refractory malignant lymphomas. *Patients and methods:* Sixty-five patients with Hodgkin's disease (HD) ($n = 14$) or non-Hodgkin's lymphomas (NHL) ($n = 51$) were enrolled in the study. The ASHAP therapy consisted of ADR (40 mg/m^2 by continuous infusion (CI) over 96 h), methylprednisolone (500 mg i.v., days 1–5), Ara-C (2 g/m^2 as a 2-h infusion on day 5), and CDDP (100 mg/m^2 by CI over 96 h). *Results:* Twenty-five patients (38%) achieved complete remission (CR) and 20 (31%) were taken into partial remission (PR) for an overall response rate of 69%. Thirty-two patients with CR or PR following ASHAP underwent high-dose therapy (HDT) with subsequent hematopoietic stem cell transplantation. After a median follow-up of 52 months, 13 patients are in continuous CR (CCR), the 3-year event-free survival (EFS) was 30% for responders and 21% for all patients. The median overall survival (OS) was 12 months (range 0–70 months), and the OS rate after 3 years was 32%. Unfavorable prognostic factors for EFS and OS by univariate analysis were an elevated value of the serum lactate dehydrogenase and refractory lymphoma. The most frequently observed side effects following ASHAP were leukocytopenia and thrombocytopenia of World Health Organization (WHO) grades III/IV in approximately 80% of all courses. Non-hematological toxicities such as gastrointestinal side effects, infections, mucositis, renal and neurotoxicity occurred more rarely and reached WHO grades III/IV only occasionally. No treatment-related mortality with ASHAP was observed. *Conclusions:* ASHAP is an effective and moderately toxic salvage therapy for patients with recurrent or refractory HD and NHL. The results in patients responding to ASHAP and afterwards undergoing HDT with stem cell support are comparable with other established protocols and indicate an improvement in survival if HDT is carried out as intensification.

Key words Hodgkin's disease · Non-Hodgkin's lymphoma · Salvage therapy · ASHAP protocol · High-dose therapy · Autologous stem cell transplantation

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Introduction

The prognosis of patients with Hodgkin's disease (HD) and non Hodgkin's lymphoma (NHL) in relapse or in those resistant to therapy is very poor [1, 2]. Although different salvage protocols (IMVP-16, MIME, MINE, CEP, CEVD) led to complete remission (CR) rates up to 40%, long-term remissions were observed in only approximately 10–20% of the patients [3–7]. Using regimens such as mini-BEAM or

Dexa-BEAM in HD, response rates of more than 60% have been reported, and long-term disease-free survival (DFS) of 25% seemed to be achievable [8, 9]. Employing high-dose therapy (HDT), it was possible to improve the long-term survival up to 40–50% [8–13]; however, significant differences were observed between patients having a sensitive relapse and those with refractory lymphomas whose benefit of HDT was markedly lower [10–13].

Based on the observation that cisplatin (CDDP) as single agent induced remissions in about 20% [14, 15], CDDP-containing protocols such as PEB, DHAP, or ESHAP were developed on the basis of established in vitro synergisms [e.g., with etoposide (VP-16) or cytarabine (Ara-C)] [16–19]. With these protocols, a response rate of up to 70% with CR rates of up to 37% was observed, even though the overall survival was not substantially improved [17–23]. The ASHAP protocol has been developed substituting adriamycin (ADR) for VP-16, and the remission data achieved using this protocol (response up to approximately 80%, CR rate of approximately 45%) suggested an improvement in comparison to ESHAP [24–26].

Patients and methods

Patients

A total of 65 patients, 28 with recurrent and 37 with refractory lymphomas, were treated with ASHAP during the period from May 1991 to March 1995. Two of the patients were suffering from secondary NHL on the basis of a preexisting HD. Stage III or IV was present in approximately 75% of the patients, and about 30% of the patients showed B-symptoms. Lactate dehydrogenase (LDH) prior to ASHAP therapy was elevated in more than 50% of the patients whose LDH value was known. In addition, more than half of the patients exhibited an extranodal involvement, with at least two localisations in 11 patients (17%), in whom particularly the lungs, pleura, skin, and skeleton were invaded. All patients had been intensively pretreated. Three patients had received autologous bone marrow transplantation. Almost half of the patients had been treated according to two or more regimens. Nearly all had already been treated previously with ADR (Table 1).

Table 1 Patient characteristics. *NHL* non-Hodgkin's lymphoma

Characteristics	Patients
No. of patients	65
Age (years)	
Median	40
Range	17–76
Male/female	33/32
Histology	
Hodgkin's disease	14 (21%)
Low-grade (LG) NHL	13 (20%)
High-grade (HG) NHL	38 (59%)
Stage	
I	3 (5%)
II	14 (21%)
III	18 (28%)
IV	30 (46%)
B-symptoms	20 (31%)
Extranodal involvement	37 (57%)
One localisation	26 (40%)
> One localisation	11 (17%)
Serum LDH	
Normal	22 (34%)
Elevated	25 (38%)
Unknown	18 (28%)
Prior Chemotherapy	
One regimen	33 (51%)
Two regimens	14 (21%)
> Two regimens	18 (28%)
Adriamycin pretreatment	63 (97%)
VP-16 pretreatment	50 (77%)
Cytarabine pretreatment	14 (21%)
Cisplatin pretreatment	3 (5%)
Prior radiotherapy	32 (49%)
Prior high-dose therapy	3 (5%)
Recurrent lymphomas	28 (43%)
Early relapse (after $\leq$ 12 months)	18 (28%)
Late relapse (after > 12 months)	10 (15%)
First relapse	22 (34%)
$\geq$ 3 Second relapse	6 (9%)
Refractory lymphomas	37 (57%)
Primary refractory	28 (43%)
Refractory relapse	9 (14%)

Inclusion and exclusion criteria

Patients were included in the ASHAP study with histologically proven or mediastinal relapse, respectively, of preexisting HD or NHL, with cytologically proven relapse of a diffuse NHL, and with histologically proven HD/NHL and refractory/progressive olisease to primary or relapse therapy. Histopathological NHL nomenclature was used according to the Kiel classification [27]. An evaluable (i.e., measurable) disease was required, with the exception of those cases in which the lymphoma had been removed in toto for histological confirmation. Patients were at least 16 years of age, and the upper age limit for the application of HDT was 60 years. In addition, an adequate performance status (Karnofsky index > 60%) was required in connection with a life expectancy of more than 12 weeks. The previously administered cumulative ADR dose should have been less than 350 mg/m^2. Prior cytostatic treatment was obligatory; however, no chemotherapy, immunotherapy, or radiotherapy was permitted during the preceeding 2 weeks. Further exclusion criteria were any invasion of the central nervous system (CNS) and substantial restrictions of cardiac [clinical, electrocardiogram (ECG), technetium scan, restricted by 50% or more], pulmonary (vital capacity or diffusion capacity > 70% of the required value), hepatic (bilirubin > 34 μmol/l or 2.0 mg%), and renal (creatinine > 170 μmol/l or 1.9 mg%) functions.

Treatment plan

The design of the ASHAP protocol was approved by the local ethics committee, Hamburg. ASHAP therapy was performed in hospital and, in each case, the written consent of the patient had to be obtained.

First, the patients received two cycles of ASHAP, and upon insufficient response (tumor regression of less than 50%) or progression an alternative therapy was initiated. Consolidant HDT was scheduled for patients with response to ASHAP (CR/PR) where at least two cycles should have been carried out. The choice of the transplantation method (allogeneic or autologous bone marrow transplantation, autologous peripheral blood stem cell transplantation) and conditioning regimen were determined by the transplanting center. The ASHAP protocol was performed including hydration with 1 : 1 NaCl 0.9% : glucose 5% solution, first administered 6 h prior to CDDP infusion in an amount of 750 ml/m^2, afterwards in parallel to CDDP infusion

Table 2 ASHAP regimen

Drug	Dose	Frequency	Application/Duration
Adriamycin	10 mg/m^2 (total of 40 mg/m^2)	Days 1–4	i.v. (CI)
Solumedrol	500 mg	Days 1–5	i.v.
Cytarabine	2 g/m^2	Day 5	i.v. (2 h)
Cisplatin	25 mg/m^2 (total of 100 mg/m^2)	Days 1–4	i.v. (CI)
Granulocyte-stimulating factor	5 μg/kg/day s.c./i.v. from day 6 until granulocytes >3.0 Gpt/l on three successive days		

in an amount of 2.5 l/m^2/day and upon addition of 20 mval KCl/l. The treatment plan of ASHAP therapy is listed in Table 2.

ASHAP therapy was scheduled to be repeated on day 21, according to protocol, provided that the leukocyte or platelet counts had recovered to more than 3.0 Gpt/l or 100 Gpt/l, respectively. Dose modifications for CDDP/Ara-C/ADR or CDDP alone upon occurrence of myelotoxicity or nephrotoxicity were determined by the study protocol. A restaging was required within 21 days after starting the second ASHAP cycle.

High-dose chemotherapy was performed in 32 patients [$n=7$ HD patients and $n=25$ NHL patients (7 low-grade NHL, 18 high-grade NHL)]. Conditioning was performed in seven cases by a total body irradiation (TBI)-containing regimen, while 25 patients exclusively received high-dose chemotherapy. Generally, the combination of busulfan/cyclophosphamide/etoposide was employed most frequently (18 patients). For 29 patients, peripheral blood stem cells were used as a stem cell source, while one patient underwent autologous and two further patients underwent allogeneic bone marrow transplantation.

Statistical analysis

The duration of CR was evaluated starting from the detection of a complete remission, while the duration of event-free survival (EFS) or overall survival (OS) were calculated from the start of ASHAP therapy. EFS and OS were tabulated using the method of Kaplan and Meier [28]. The effect of different factors on EFS and OS was tested using univariate analysis and the Fisher's exact test or the log rank test, respectively [29].

Results

Response to ASHAP

Sixty-five patients were treated with a median of two cycles of ASHAP (range 1–5). Twenty-five of the patients (38%) achieved CR, and partial remission (PR) occurred in 20 patients (31%), corresponding to a response rate of 69%. Sixteen patients with CR achieved this response as early as after two ASHAP cycles (64%); only six and three (24% and 12%) reached a CR after three or four ASHAP cycles. HD and NHL achieved comparable response rates. Markedly lower remission rates occurred upon an initially increased LDH and in the cases of refractory lymphomas (especially primary resistant diseases). The therapy results achieved are presented in Table 3.

Toxicity

The toxicity observed was generally moderate, and no deaths were observed in relation to salvage therapy. The death of one female patient was caused by acute transplantation-associated toxicity [veno-occlusive disease (VOD)]. The main toxicity following ASHAP occurred in the area of hematopoiesis, with granulocytopenias or thrombocytopenias of World Health

Table 3 Therapy results. *NHL* non-Hodgkin's lymphoma; *LDH* lactate dehydrogenase

	No.	CR rate		PR rate		Response	
		No.	%	No.	%	No.	%
HD	14	3	21	6	43	9	64
Low-grade NHL	13	6	48	4	31	10	77
High-grade NHL	38	16	42	10	26	26	68
Relapse	28	19	68	6	21	25	89
Refractory	37	6	16	14	38	20	54
Early relapse	18	12	67	3	17	15	83
Late relapse	10	7	70	3	30	10	100
1st relapse	22	14	64	5	22	19	86
After 1st relapse	6	5	83	1	17	6	100
Primary refractory	28	3	11	8	29	11	40
Refractory relapse	9	3	33	6	67	9	100
Stages I–III	35	18	51	8	23	26	74
Stage IV	30	7	23	12	40	19	63
B symptoms	20	5	25	8	40	13	65
No B symptoms	45	20	44	12	27	32	71
E involvement	37	11	30	13	35	24	65
No E involvement	28	14	50	7	25	21	75
Normal LDH	22	9	41	7	32	16	73
Elevated LDH	25	7	28	7	28	14	56

Table 4 Toxicity following ASHAP

Hematoxicity	WHO-I	WHO-II	WHO-III	WHO-IV
Granulocytopenia	7.0%	4.7%	11.6%	69.7%
Thrombocytopenia	5.0%	6.7%	8.9%	71.1%
Non-hematological toxicity	**WHO-I/II**	**WHO-III/IV**	**Total**	
Nausea	20.9%	3.7%	24.6%	
Stomatitis/mucositis	10.4%	1.5%	11.9%	
Infections	6.7%	1.5%	8.2%	
Diarrhea	7.5%	–	7.5%	
Neurotoxicity	6.8%	0.7%	7.5%	
Nephrotoxicity	6.0%	0.7%	6.7%	
Pain	6.0%	–	6.0%	
Cardiotoxicity	5.2%	–	5.2%	
Elevated transaminases	5.2%	–	5.2%	

organization (WHO) grades III/IV in approximately 80% of all cycles. Generally, no erythrocyte or platelet substitution was necessary (median 0, range 0–7 and 0–8, respectively). A cumulative increase in hematotoxicity during several ASHAP cycles was not observed. The remaining organotoxicities were comparable with those known from other salvage therapies and at maximum reached WHO grade III with the exception of individual severe courses of mucositis/stomatitis, polyneuropathy in the sense of Guillain-Barre syndrome, and infections of central venous catheters. Most frequently, nausea, mucositis/stomatitis, and neutropenic infections were observed (Table 4).

Outcome

Of 45 responders following ASHAP, 32 (18 CR/14 PR) were consolidated by HDT, while 9 of the patients either rejected HDT or HDT was abandoned because of contraindications, and four of the patients with early progression following PR were introduced to HDT after they had responded to an alternative salvage therapy. After a median follow-up for all responders of 49 months, 13 live in continuous CR (CCR). Of thirty patients who suffered relapse or progression, five are still alive (one patient again in CCR following further chemotherapy) and 25 died. Two patients died of other causes, one of a secondary malignoma (colon carcinoma) and another of VOD caused by HDT. Of the 20 patients who had achieved less than a PR following ASHAP, two patients are in CCR after further therapy and 18 patients have died of their disease. Thus, a total of one-fifth of the patients is in CCR with a median follow-up of 52 months. The median EFS was 6 months, and the 3-year EFS was 21%. The median OS was 12 months (range 0–70 months), while the 3-year OS was 32%, and a plateau at 28% was observed after 46 months (Fig. 1).

Thirty-two patients received high-dose chemotherapy with stem cell support. The 3-year EFS and OS were 37% and 47%, respectively. After a median follow-up of 47 months, 12 patients are in CCR. The remission state prior to HDT (CR vs PR) led to differing results, especially with respect to the 3-year EFS (44% vs 27%, $P = 0.35$) while the 3-year OS was similar (50% vs 43%, $P = 0.63$). The differences showed no statistical significance and, particularly for the 3-year EFS, the difference of 17% in favor of HDT is presumably related to the smaller number of cases (Fig. 2).

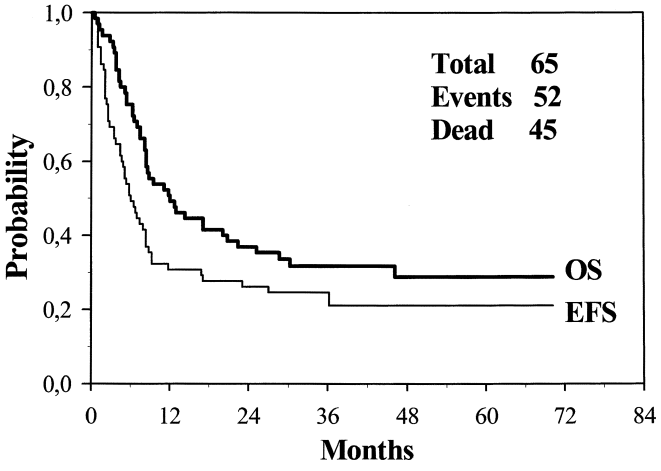

Fig. 1 Overall survival (OS) and event-free survival (EFS) of patients treated with ASHAP; 3-year rate for OS and EFS, respectively, is 32% and 21%; events included treatment failure (relapse, progressive disease), one secondary cancer (colon carcinoma) and one patient with veno-occlusive disease (VOD) after high-dose therapy (HDT)

Prognostic factors

The examination of different factors with respect to their prognostic significance for EFS and OS showed highly significant differences of elevated versus normal LDH (EFS $P = 0.008$ and OS $P = 0.0003$) or refractory versus responsive lymphomas (EFS $P = 0.001$ and OS $P = 0.026$) (Fig. 3 and Fig. 4).

Among the relapses, patients with late relapse have a significantly improved OS and form the only subgroup in the evaluation where the median OS has not been reached until now. Although stage IV prior to

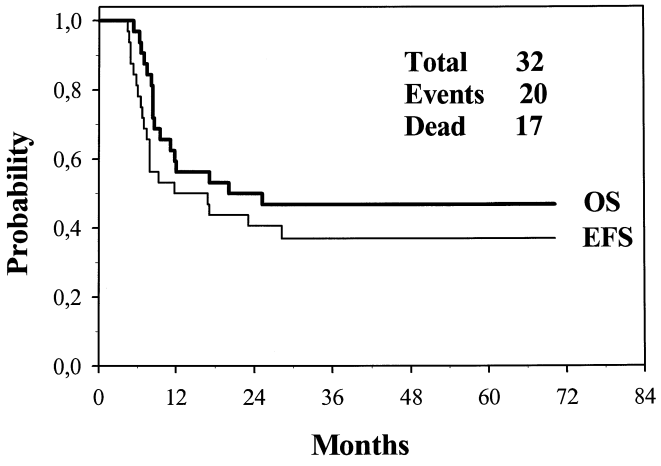

Fig. 2 Event-free survival (EFS) and overall survival (OS) of 32 patients responding to ASHAP and consolidated by subsequent high-dose therapy (HDT)/stem cell transplantation (SCT)

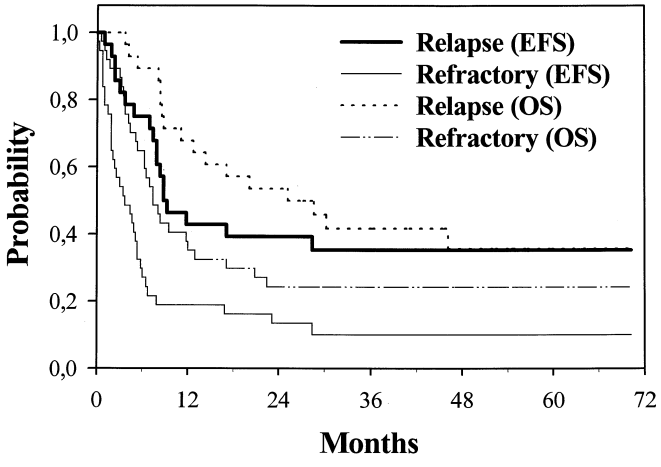

Fig. 3 Survival curves for patients with relapsed or refractory lymphoma treated with ASHAP [$P = 0.01$ EFS; $P = 0.03$ OS]

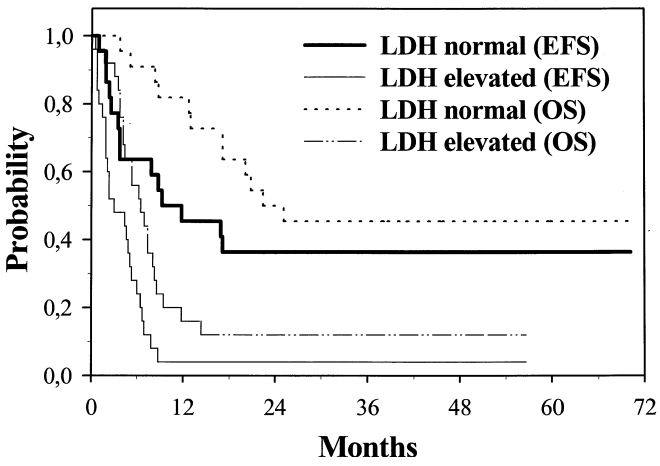

Fig. 4 Event-free survival (EFS) and overall survival (OS) for patients with normal and elevated lactate dehydrogenase (LDH) values treated with ASHAP ($P = 0.008$ and $P = 0.0003$, respectively)

therapy was suggestive of being a relevant factor for EFS and OS, the level of significance was missed ($P = 0.063$ and $P = 0.078$, respectively). No significant differences were found between the various histological subgroups. Patients with CR exhibited improved 3-year EFS and OS data if the CR had already been achieved after one to two ASHAP cycles (CR 1–2) or if HDT consolidation was performed following CR. However, these differences could not be statistically confirmed because the number of cases was too small (Table 5).

Discussion

The prognosis of patients with primary resistant or recurrent lymphomas is unfavorable. This applies to

Table 5 Prognostic factors. *NHL* non-Hodgkin's lymphoma; *EFS* event-free survival; *OS* overall survival; *n.s.* not significant; *LDH* lactate dehydrogenase; *CR* complete remission; *HDT* high-dose therapy

	Patients	3-year EFS (%)	*P* value	3-year OS (%)	*P* value
Hodgkin's disease	14	14	n.s.	34	n.s.
Low-grade NHL	13	21		46	
High-grade NHL	38	23		26	
Relapse	28	35	0.001	42	0.026
Refractory	37	10		24	
1st relapse	22	36	n.s.	44	n.s.
After 1st relapse	6	33		33	
Early relapse	18	28	n.s.	26	0.017
Late relapse	10	50		70	
Primary refractory	28	11	0.021	21	n.s.
Refractory relapse	9	11		33	
Stages I–III	35	28	n.s.	41	n.s.
Stage IV	30	13		20	
Normal LDH	22	36	0.0008	45	0.0003
Elevated LDH	25	4		12	
CR 1–2	16	43	n.s.	48	n.s.
CR 3–4	9	33		33	
CR + HDT	18	44	n.s.	50	n.s.
CR without HDT	7	29		29	
CR prior HDT	18	44	n.s.	50	n.s.
PR prior HDT	14	27	n.s.	43	n.s.

about 30–50% of the patients with advanced HD and to up to 70% of patients with intermediate/high-grade NHL. While various conventional salvage protocols (IMVP-16, MIME, MINE, CEP, CEVD) were able to achieve CR rates up to approximately 40%, only 10–20% of the patients persisted disease-free [3–7]. Response rates of more than 60% were described for the dose-intensified Dexa-BEAM protocol, the freedom from treatment failure (FFTF) for patients with HD after a median follow-up of 32 months being 25% (41 events in 55 patients) [9]. In addition, markedly different results regarding response and survival were obtained for patients with primary refractory disease and early or late relapse [9].

Starting from a response rate of 20% in monotherapy [14, 15], trials of CDDP in the salvage therapy of malignant lymphomas were conducted in the 1980s. The drug combinations based on different synergisms of CDDP yielded response rates up to about 80% [30–33]. On the basis of these results, the DHAP protocol was developed, and Velasquez et al. reported in 90 patients with recurrent (38) and refractory (52) NHL, CR rates and response rates of 31% and 55%, respectively, as well as a 3-year OS of 17% [18, 34]. A highly increased LDH value and a high tumor burden had the highest prognostic value for response and survival under DHAP [18]. The subsequent protocol, ESHAP, achieved a CR rate of 37% in 122 NHL patients with refractory disease as well as early and late recurrences [16]. The 3-year OS was 31%. Significantly negative prognostic factors for CR rate and 3-year OS were refractoriness (no previous CR), an elevated LDH value, and a high tumor burden. In comparison with DHAP, ESHAP was considered to be more effective and, in particular, less toxic [19, 34]. Substituting adriamycin for etoposide (96-h CI), the ASHAP protocol was developed [24], which besides a reduction of toxicity was particularly aimed at an improvement of response, since certain tumor cells are less resistant upon continuous low dose cytostatic exposure compared with high dose bolus administration [35, 36] which for example could also explain the good results achieved by EPOCH [36]. The ASHAP data of Velasquez et al. showed a response rate of 85%, a CR rate of 45%, and an OS of 40%, with a median follow-up of 19 months [24, 26].

Our results with ASHAP also demonstrate clearly the efficacy of this protocol in recurrent and refractory lymphomas. The CR rate of 43% achieved in NHL and the freedom from disease of 27% and 23% of all 51 NHL patients treated by ASHAP after 2 years and 3 years, respectively, are at least equivalent to other established salvage protocols, such as IMVP-16, MIME, MINE, or EPOCH [3–5, 37] and the platinum-containing protocols DHAP and ESHAP or MINE–ESHAP [18–23, 38]. Therapy results upon HD were also of interest, although this applied to only a small group of altogether 14 patients. However, these patients had undergone intensive pretreatment (eight patients had already received Dexa-BEAM) and the prognosis seemed to be unfavorable in most of the cases (eight refractory HD, four early relapses). The response rate of 64% achieved and the 3-year EFS and OS of 14% and 34%, respectively, are comparable with the results of Rodriguez et al. [39] and may indicate that, upon failure of an established second-line therapy such as Dexa-BEAM, the application of ASHAP represents an alternative therapy option for patients with HD.

Regarding the entirety of 65 patients treated by ASHAP, the remission as well as survival data (69% response with 38% CR, 3-year EFS and OS of 21% and 32%, respectively) were comparable with other established salvage protocols. The most important prognostic factors for long-term freedom from disease and overall survival proved to be an elevated LDH value and refractory behavior of the lymphomas towards previous therapy as already reported for other recurrence therapies such as DHAP, ESHAP, or Dexa-BEAM [9, 18, 19].

Main toxicity observed with ASHAP was myelosuppression. Non-hematological side effects were mostly moderate and only in rare cases exceeded WHO grade II. Compared with DHAP and Dexa-BEAM, ASHAP seems to be less toxic, the toxicity data being similar to that of ESHAP [9, 18, 19].

The question of benefit of and most suitable time for HDT in the frame of the salvage strategy in malignant lymphomas has repeatedly been the subject of clinical studies since the 1980s [2, 10, 40–44]. The results of the PARMA study have shown that in chemotherapy-sensitive relapses a consolidant HDT has significant advantages in EFS (46% vs 12%, $P = 0.001$) as well as overall survival (53% vs 32%, $P = 0.038$) compared with an exclusively conventional salvage therapy [45]. This is also evident with regard to the data of 3750 evaluated cases of the European Bone Marrow Transplantation Group (EBMT) lymphoma registry in which 5-year progression free survival (PFS) values of 43.3% and 29.1% have been observed in patients with HG-NHL in the second or subsequent CR or with chemosensitive disease, respectively [46]. Regarding the otherwise disappointing results with recurrent HG-NHL having a long-term DFS of approximately 5–10% [47], this may be further evidence in favor of the benefit of a consolidant HDT in chemosensitive recurrent NHL. In the area of HD, it was also shown that a significantly longer time to treatment failure (TTF) for patients with chemosensitive relapse consolidated by HDT in comparison with dose-intensified salvage therapy employing growth factors (Dexa-BEAM) [48]. Chemosensitivity of the lymphoma towards a previous conventional salvage therapy has been repeatedly proven to be the most important prognostic factor for the long-term benefit of a HDT in NHL and HD [49–54]. The remission state prior to HDT is a factor of high prognostic significance, as already described by Philip et al. in 1987

[10]. Differences of similar significance have already resulted from the above-mentioned EMBT evaluation for patients with HD and HG-NHL in whom, in contrast to the good results with chemosensitive lymphomas for refractory diseases, 5-year PFS rates of less than 20% were achieved [46]. Also in our patients the remission state prior to HDT (CR vs PR) led to differences, in particular with respect to PFS; however, the significance level was missed because of a too small number of cases.

In summary, ASHAP is an effective salvage therapy for patients with recurrent or refractory HD and NHL. Significant prognostic factors for event-free and overall survival are an elevated LDH value and the refractoriness to previous chemotherapy. The toxicity associated with ASHAP is moderate with short-term myelosuppression. Upon achievement of CR or PR following ASHAP, these patients seem to gain from a subsequent HDT accompanied by stem cell support.

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References

1. Longo DL, Duffey PL, Young RC, Hubbard SM, Ihde DC, Glatstein E, Phares JC, Jaffe ES, Urba WJ, De Vita VT, Jr (1992) Conventional-dose salvage combination chemotherapy in patients relapsing with Hodgkin's disease after combination chemotherapy: the low probability for cure. J Clin Oncol 10:210–218
2. Gisselbrecht C, Bosly A, Lepage E, Reyes F, Philip T, Haioun C, Tilly H, Coiffier B (1993) Autologous hematopoietic stem cell transplantation in intermediate and high grade non-Hodgkin's lymphoma: a review. Ann Oncol 4[suppl 1]:7–13
3. Cabanillas F, Hagemeister FB, Bodey GP, Freireich EJ (1982) IMVP-16: an effective regimen for patients with lymphoma who have relapsed after initial chemotherapy. Blood 60:693–697
4. Cabanillas F, Hagemeister FB, McLaughlin P, Velasquez WS, Riggs S, Fuller L, Smith T (1987) Results of MIME salvage regimen for recurrent or refractory lymphoma. J Clin Oncol 5:407–412
5. Rodriguez MA, Cabanillas F, Hagemeister FB, Mc Laughlin P, Romaguera JE, Swan F, Velasquez WS (1995) A phase II trial of mesna / ifosfamide, mitoxantrone and etoposide for refractory lymphomas. Ann Oncol 6:609–611
6. Santoro A, Viviani S, Bonfante V, Valagussa P, Bonadonna C (1987) CEP in Hodgkin's disease (HD) resistant to MOPP and ABVD (abstract). Proc Am Soc Clin Oncol 6:199
7. Pfreundschuh MG, Schoppe WD, Fuchs R, Pflüger KH, Löffler M, Diehl V (1987) Lomustine, etoposide, vindesine, and dexamethasone (CEVD) in Hodgkin's lymphoma refractory to cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) and doxorubicin, bleomycin, vinblastine, and darcabazine (ABVD): a multicenter trial of the German Hodgkin's Study Group. Cancer Treat Rep 71:1203–1207
8. Chopra R, Linch DC, McMillan AK, Blair S, Patterson KG, Moir D, Richards JDM, Cervi P, Kinsey S, Goldstone AH (1992) Mini-BEAM followed by BEAM and ABMT for very poor risk Hodgkin's disease. Br J Haematol 81:197–202
9. Pfreundschuh MG, Rueffer U, Lathan B, Schmitz N, Brosteanu O, Hasenclever D, Haas R, Kirchner H, Koch P, Kuse R, Loeffler M, Diehl V (1994) Dexa-BEAM in patients with Hodgkin's disease refractory to multidrug chemotherapy regimes: a trial of the German Hodgkin's Disease Study Group. J Clin Oncol 12:580–586
10. Philip T, Armitage JO, Spitzer G, Chauvin F, Jagannath S, Cahn JY, Colombat P, Goldstone AH, Gorin NC, Flesh M, Laporte JP, Maraninchi D, Pico J, Bosly A, Anderson C, Schots R, Biron P, Cabanillas F, Dicke K (1987) High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. N Engl J Med 316:1493–1498
11. Cabanillas F, Velasquez WS, McLaughlin P, Jagannath S, Hagemeister FB, Redman JR, Swan F, Rodriguez MA (1988) Results of recent salvage chemotherapy regimes for lymphoma and Hodgkin's disease. Semin Hematol 25[suppl 2]:47–50
12. Appelbaum FR, Thomas ED (1989) Review of the use of marrow transplantation in the treatment of non-Hodgkin's lymphomas. J Clin Oncol 7:440–447
13. Armitage JO (1992) Autologous bone marrow transplantation for Hodgkin's disease. Ann Oncol 3[suppl 4]:95–96
14. Rossof AH, Coltman Jr CA, Jones SE, Talley RW (1979) Phase II evaluation of cis-dichlorodiammineplatinum(II) in lymphomas: a Southwest Oncology Group Study. Cancer Treat Rep 63:1605–1608
15. Cavalli F, Jungi WF, Nissen NI, Pajak TF, Coleman M, Holland JF (1981) Phase II trial of cis-dichlorodiammineplatinum(II) in advanced malignant lymphoma: a study of the cancer and acute leukemia group B. Cancer 48:1927–1930
16. Bergerat JP, Drewinko B, Corry P, Barlogie B, Ho HD (1981) Synergistic lethal effect of cis-dichlorodiammine-platinum and 1-βb-D-arabinofuranosylcytosine. Cancer Res 41:25–30
17. Comella P, Abate G, Di Finizio G, Daponte A, Zarrilli D (1990) Treatment of resistant non-Hodgkin's-lymphoma with cisplatin, etoposide, and bleomycin. Cancer Chemother Pharmacol 26:306–309
18. Velasquez WS, Cabanillas F, Salvador P, Mc Laughlin P, Fridrik M, Tucker S, Jagannath S, Hagemeister FB, Redman JR, Swan F, Barlogie B (1988) Effective salvage therapy for lymphoma with cisplatin in combination high-dose Ara-C and dexamethasone (DHAP). Blood 71:117–122
19. Velasquez WS, McLaughlin P, Tucker S, Hagemeister FB, Swan F, Rodriguez MA, Romaguera J, Rubenstein E, Cabanillas F (1994) ESHAP-an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol 12:1169–1176
20. Brandwein JM, Callum J, Sutcliffe SB, Scott JG, Keating A (1990) Evaluation of cytoreductive therapy prior to high dose treatment with autologous bone marrow transplantation in relapsed and refractory Hodgkin's disease. Bone Marrow Transplant 5:99–103
21. Press OW, Livingston R, Mortimer J, Collins C, Appelbaum F (1991) Treatment of relapsed non-Hodgkin's lymphoma with dexamethasone, high-dose cytarabine, and cisplatin before marrow transplantation. J Clin Oncol 9:423–431
22. Zinzani PL, Martelli M, Tura S, Mandelli F (1993) Granulocyte colony stimulating factor (G-CSF) as adjunct therapy in relapsed-resistant high-grade non-Hodgkin's lymphoma. Haematologica 78:40–43
23. Ezzat AA, Khalifa F, Berry J, Khan B, Raja MA, Abdel-Warith A (1994) ESHAP: an effective treatment in selected patients with relapsed non-Hodgkin's lymphoma. Ann Oncol 5:453–546
24. Velasquez WS, Dunphy F, Santillana S, Adkins D, Bowers C, Broun Jr GO, Petruska PJ, Spitzer G (1993) ASHAP, an effective treatment for relapsing and refractory Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) (abstract). Blood 82[suppl 1]:138a

25. Peters SO, Schmitz N, Metzner H, Illiger HJ, Schubert JC, Weh HJ, Hossfeld DK, Zander AR (1993) Adriamycin, cisplatin, ara-c and methylprednisolone (ASHAP) combination chemotherapy in relapsed and refractory lymphoma and Hodgkin's disease – preliminary data (abstract). Blood 82[suppl 1]:574a
26. Velasquez W, Dunphy F, Petruska P, Adkins D, Broun G, Jr, Spitzer G (1995) ASHAP with or without ABMT for high risk non-Hodgkin's lymphoma (NHL) (abstract). Proc ASCO 14:387
27. Lennert K, Mohri N, Stein H, Kaiserling E (1975) The histopathology of malignant lymphoma. Br J Haematol 31[suppl]:193–203
28. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assess 53:457
29. Peto R, Peto J (1972) Asymptotically efficient rank invariation test procedures (with discussion). J R Stat Soc A 135:185
30. Liepman MK, Wheeler RH, Zuckerman KS, Lobuglio AF (1982) Combination chemotherapy of refractory lymphoma with cis-dichlorodiammineplatinum, vinblastine, and bleomycin. Cancer 50:2736–2739
31. Corder MP, Clamon GH (1984) Salvage therapy of aggressive non-Hodgkin's lymphoma with a combination of vinblastine, bleomycin, and cisplatin. Cancer 54:202–206
32. Judson IR, Wiltshaw E (1985) Cis-dichlorodiammineplatinum (cis-platinum) and etoposide (VP-16) in malignant lymphoma – an effective salvage regimen. Cancer Chemother Pharmacol 14:258–261
33. Tubiana N, Lejeune C, Horchowski N, Gastaut JA, Finaud M, Sainty D, Sebahoun G, Carcassonne Y (1987) Etoposide and cisplatinum in resistant lymphomas. Cancer Chemother Pharmacol 20:179–180
34. Rodriguez-Monge EJ, Cabanillas F (1997) Long-term follow-up of platinum based lymphoma salvage regimens. The M.D. Anderson Cancer Center Experience. Hematol Oncol North Am 11:937–947
35. Lai GM, Chen YN, Mickley LA, Fojo AT, Bates SE (1991) P-glycoprotein expression and schedule dependence of adriamycin cytotoxicity in human colon carcinoma cell lines. Int J Cancer 49:669–673
36. Zhan Z, Kang YK, Regis J, Shives B, Bryant G, Wilson W, Fojo AT, Bates S (1993) Taxol resistance: in vitro and in vivo studies in breast cancer and lymphoma (abstract). Proc Am Assoc Cancer Res 34:215
37. Wilson WH, Bryant G, Bates S, Fojo A, Wittes RE, Steinberg SM, Kohler DR, Jaffe ES, Herdt J, Cheson BD, Chabner BA (1993) EPOCH Chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. J Clin Oncol 11:1573–1582
38. Rodriguez MA, Cabanillas FC, Velasquez WS, Hagemeister FB, McLaughlin P, Swan F, Romaguera JE (1995) Results of a salvage treatment program for relapsing lymphoma: MINE consolidated with ESHAP. J Clin Oncol 13:1734–1741
39. Rodriguez J, Rodriguez MA, Fayad L, Hagemeister B, McLaughlin P, Swan F, Sarris A, Romaguera J, Andersson B, Cabanillas F (1998) ASHAP is an effective salvage regimen in patients with refractory or recurrent Hodgkin's disease. Blood 93:3632–3636
40. Desch CE, Lasala MR, Smith TJ, Hillner BE (1992) The optimal timing of autologous bone marrow transplantation in Hodgkin's disease patients after a chemotherapy relapse. J Clin Oncol 10:200–209
41. Bosly A, Coiffier B, Gisselbrecht C, Tilly H, Auzanneau G, Andrien F, Herbrecht R, Legros M, Devaux Y, Jaubert J, et al. (1992) Bone marrow transplantation prolongs survival after relapse in aggressive-lymphoma patients treated with the LNH-84 regimen. J Clin Oncol 10:1615–1623
42. Linch DC, Winfield D, Goldstone AH, et al. (1993) Dose intensification with autologous bone marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet 341:1051–1054
43. Coiffier B, Bosly A, Tilly H, sebban C, Herbrecht R, Gisselbrecht C (1994) Long-term outcome of aggressive lymphoma patients treated with the LNH-84 protocol: relapsing patients may be salvaged by intensive therapy with stem cell transplantation (ITwSCT) (abstract). Proc ASCO 13:372
44. Meehan KR, Pritchard RS, Leichter JW, Littenberg B, Welch HG (1995) Autologous bone marrow transplantation versus chemotherapy in relapsed/refractory non-Hodgkin's lymphoma: estimates of long-term survival from the recent literature. Am J Hematol 50:116–123
45. Philip T, Guglielmi C, Hagenbeek A, Somers R, van der Lelie H, Bron D, Sonneveld P, Gisselbrecht C, Cahn JY, Harousseau JL, Coiffier B, Biron P, Mandelli F, Chauvin F (1995) Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 333:1540–1545
46. Fielding AK, Pearce RM, Taghipour G, et al. (1997) Autologous transplantation for lymphoma – trends over 15 years from 3750 cases reported to the EBMT lymphoma registry. What have we learned? In: Schmitz N (ed) Rezidivtherapie hochmaligner Non-Hodgkin-Lymphome. Internist 38:143–149
47. Armitage JO (1993) Treatment of non-Hodgkin's lymphoma. N Engl J Med 328:1023–1030
48. Schmitz N, Sextro M, Hasenclever D, Carella A, Fiedler F, Schlimok G, Hossfeld DK, Diehl V (1997) HD-R1: first results of a randomized trial comparing aggressive chemotherapy with high-dose therapy (HDT) and hematopoietic stem cell transplantation (HSCT) in patients with chemosensitive relapse of Hodgkin's disease (HD) (abstract). Blood 90[suppl 1]:115a
49. Vose JM, Anderson JR, Kessinger A, Bierman PJ, Coccia P, Reed EC, Gordon P, Armitage JO (1993) High-dose chemotherapy and autologous hematopoietic stem cell transplantation for aggressive non-Hodgkin's lymphoma. J Clin Oncol 11:1846–1851
50. Wheeler C, Strawderman M, Ayash L, Churchill WH, Bierer BE, Elias A, Gilliland DG, Antman K, Guinan EC, Eder JP, Weinstein H, Schwartz G, Ferrara J, Mazanet R, Rimm IJ, Tepler I, McCarthy P, Mauch P, Ault K, Gaynes L, McCauley M, Schnipper LE, Antin J (1993) Prognostic factors for treatment outcome in autotransplantation of intermediate-grade and high-grade non-Hodgkin's lymphoma with cyclophosphamide, carmustine, and etoposide. J Clin Oncol 11:1085–1091
51. Rapoport AP, Rowe JM, Kouides PA, Duerst RA, Abboud CN, Liesveld JL, Packman CH, Ebely S, Sherman M, Tanner MA, Constine LS, DiPersio JF (1993) One hundred autotransplants for relapsed or refractory Hodgkin's disease and lymphoma: value of pretransplant disease status for predicting outcome. J Clin Oncol 11:2351–2361
52. Mahendra P, Johnson D, Hood IM, Scott MA, Barker P, Bass G, Jestice HK, Bloxham DM, Boraks P, Wimperis JZ, Baglin TP, Marcus RE (1996) High-dose therapy and autologous stem cell rescue for poor risk and refractory lymphoma: a single centre experience of 123 patients. Bone Marrow Transplant 17:973–978
53. Prince HM, Imrie K, Crump M, Stewart AK, Girouard C, Colwill R, Brandwein J, Tsang RW, Scott JG, Sutton DM, Pantalony G, Carstairs K, Sutcliffe SB, Keating A (1996) The role of intensive therapy and autologous blood and marrow transplantation for chemotherapy-sensitive relapsed and primary refractory non-Hodgkin's lymphoma: identification of major prognostic groups. Br J Haematol 4:880–889
54. Rapoport AP, Lifton R, Constine LS, Duerst RE, Abbound CN, Liesveld JL, Packman CH, Eberly S, Raubertas RF, Martin BA, Flesher WR, Kouides PA, DiPersio JF, Rowe JM (1997) Autotransplantation for relapsed or refractory non-Hodgkin's lymphoma (NHL): long-term follow-up and analysis of prognostic factor. Bone Marrow Transplant 19:883–890