Bone Marrow Transplantation (2003) 32, 637–646

www.nature.com/bmt

Mini review

What is CD4+CD56+ malignancy and how should it be treated?

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Summary:

CD4+CD56+ malignancy is a rare neoplasm with a typical clinical pattern, an aggressive course and high early relapse rate despite good initial response to chemotherapy. In this review, the impact of different therapeutic approaches on clinical outcome has been studied. We evaluated 91 published cases and our own six patients in terms of clinical features, immunophenotype/cytogenetics and treatment outcome. Treatment was divided into four groups: (A) chemotherapy less intensive than CHOP; (B) CHOP and CHOP-like regimens; (C) therapy for acute leukemia; (D) allogeneic/autologous stem cell transplantation. The median overall survival was only 13 months for all patients. Patients with skin-restricted disease showed no difference in the overall survival from patients with advanced disease (17 and 12 months, respectively). Age $\geqslant$60 years was a negative prognostic factor. Age-adjusted analysis revealed improved survival after high-dose chemo/radiotherapy followed by allogeneic stem cell transplantation when performed in first complete remission. This therapeutic approach should be recommended for eligible patients with CD4+CD56+ malignancy. For older patients the best treatment option is still unknown.
Bone Marrow Transplantation (2003) **32,** 637–646. doi:10.1038/sj.bmt.1704215
Keywords: CD4+CD56 malignancy; stem cell transplantation; chemotherapy

CD4+CD56+ hematopoietic malignancies are now regarded as a distinct clinicopathologic entity. CD4, a glycoprotein expressed on helper T cells and a subset of monocytes and thymocytes, has been found in T cell leukemia/lymphoma and in acute myeloid leukemia. Among leukocytes, the neural cell adhesion molecule CD56 is expressed predominantly on natural killer (NK) cells and on a small subset of T cells (CD8+ cytotoxic/suppressor cells and a subgroup of $\chi\delta$-T-cells). Its expression on leukemia and lymphoma cells characterizes a heterogeneous group of malignancies. Coexpression of both antigens is very rare. The classification of CD4+CD56+ lymphomas leads to a somewhat confusing terminology for this entity: blastic/blastoid NK-cell lymphoma/leukemia, cutaneous monomorphous CD4+CD56+large cell lymphoma, agranular NK-cell lymphoma, etc. In the new WHO classification, CD4+CD56+neoplasms are probably included in the ill-defined category of blastic NK-cell lymphomas. CD4+CD56+malignancies must be distinguished from the nasal type of extranodal NK/T cell lymphomas and aggressive NK-cell leukemias that may be closely related entities occurring frequently in the Asian population (Table 1). While nasal-type NK/T cell lymphoma is characterized by preferential involvement of the nasopharynx with angiocentric and angioinvasive growth resulting in extensive coagulative necroses, aggressive NK-cell leukemia usually presents with constitutional symptoms, and leukemic course. Both tumors show CD2+CD3-CD56+ phenotype and are almost constantly associated with EBV. In contrast to CD4+CD56+ lymphoma, they often present in middle-aged females.[1–4]

The question of tumor cell origin of the CD4+CD56+ neoplasm has been debated for a long time. Some authors proposed precursor NK-cell origin, whereas others suggested that CD4+CD56+ tumor cells derived from myelomonocytic precursor cells. Petrella *et al*[5] performed extensive flow cytometric analysis in 14 cases and found very high levels of CD123 expression suggesting that this disease derives from plasmacytoid monocytes. Furthermore, some authors have described reactive CD4+CD56+ cells within kidney allografts during tubular necrosis and rejection[6] and within liver biopsies in patients with chronic active hepatitis B.[7] They hypothesized that prolonged antigen stimulation may produce this unusual phenotype. Recently, Chaperot *et al*[8] using flow cytometry and *in vitro* assays suggested that CD4+CD56+ malignancies arise from transformed cells of the lymphoid-related plasmacytoid dendritic cell subset.

Little is known about the etiology and pathogenesis of CD4+CD56+ neoplasms. EBV and human herpesvirus-6 are not detectable. Human T cell lymphotropic virus type I (HTLV-I) was found in one case,[9] while others[10–12] failed to detect this virus. In general, (latent) viral infection does not seem to play an important role in the pathogenesis of this disease.

Clinically, CD4+CD56+ neoplasms usually involve the skin, spread rapidly to extracutaneous sites, and have a

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Table 1 Differential diagnosis of CD4+CD56+ malignancy

	CD4+CD56+	*Aggressive NK-cell lymphoma/leukemia*	*Nasal and nasal-type NK-cell lymphoma*	*Blastic NK-cell lymphoma/leukemia*
Age	67 years (median)	Young	Middle-aged	Middle-aged to elderly
Sex ratio	Males predominate	No sex predilection or slight male predominance	Males predominate	No sex predilection
Involved sites	Skin, BM, LN	BM, liver, spleen	Nose, nasopharynx, palate, skin, soft tissue, GI tract, testis	Skin, LN, BM, soft tissue
Morphology	Lymphoblastoid/ pleomorphic monotonous medium-sized cells with fine chromatin	Medium-sized cells with round or irregular nuclei	Polymorphic, pleomorphic	Lymphoblastoid monotonous medium-sized cells with fine chromatin
Phenotype	CD2−/+, sCD3−, cCD3+/−, CD4+, CD56+, TdT+/−, TIA-1−, Granzyme B−	CD2+, sCD3−, cCD3−, CD4−, CD56+, TdT−, TIA-1+, Granzyme B+	CD2+, sCD3−, cCD3+, CD4−/+, CD56+, TdT−, TIA-1+, Granzyme B+	CD2−/+, sCD3−, cCD3+/−, CD4−/+, CD56+, TdT+/−, TIA-1−, Granzyme B−
Association with EBV	Extremely rare	Strong	Strong	None
TCR gene	Germline	Germline	Germline	Germline
Genetics	No specific single chromosomal aberrations, often 5q, 6q, 9, 12p, 13q, and 15q	No specific chromosomal aberrations, often del(6)	No specific chromosomal aberrations, often del(6), inv(6)	No specific chromosomal aberrations
Clinical course	Aggressive with relapse	Highly aggressive	Locally destructive to aggressive	Aggressive

poor outcome. Therapeutic strategies vary widely from symptomatic treatment and local radiation therapy to allogeneic stem cell transplantation, but optimal treatment remains to be defined.

Since Adachi *et al*[10] reported the first CD4+CD56+ malignancy in 1994, 91 cases have been published (Table 2). This review summarizes the clinical and phenotypic features and treatment outcome for the malignancy including our own six patients.

Clinical features

CD4+CD56+ neoplasms generally affect older patients with a median age of 67 years (range 6–89 years). Males are affected almost three times as often as females (m:f ratio: 2.7:1). The clinical manifestations of this disease show a characteristic pattern. The vast majority of patients initially presents with cutaneous lesions of nonspecific morphology and distribution. At diagnosis, in almost 80% of patients, the disease has already spread to extracutaneous sites, most frequently to bone marrow and lymph nodes (>50% each), followed by spleen and liver (11–20%). Other organs such as nasopharynx, tonsils, CNS, lacrimal glands, muscle, or gynecological tract are only sporadically affected.

According to the Ann Arbor classification, 24% of patients are diagnosed in stage I (with only a single skin lesion), 7% patients in stage II, 2% patients in stage III, and 66% patients in stage IV. In contrast to other lymphoid malignancies, B symptoms such as fever, night sweat, and weight loss are rare.

Immunophenotype and cytogenetics

Morphologically, the malignant cells consist of monomorphic medium-sized blasts with finely dispersed chromatin. These cells consistently express CD4 and CD56, while (surface) CD3 and B cell markers are absent. HLA-DR usually is found, whereas CD8 expression is normally negative. Further NK-cell (CD16, CD57) or myeloid (eg CD34) markers are absent. Pan-T cell markers as CD2, CD5, and CD7 are rarely expressed. Phenotypic data are summarized in Table 3. Expression of T cell markers other than CD4 (eg CD5, CD7, CD8) does not influence clinical course. T cell marker positive and negative patients (balanced according to age and gender) show identical overall survival curves (data not shown). Studies for EBV by immunohistochemistry (latent membrane protein) or *in situ* hybridization of EBV-encoded RNA (EBER probes) are negative except for two cases indicating no association with EBV infection.

The genetic alterations in CD4+CD56+ neoplasms are largely unknown and in many studies cytogenetic data are missing. However, some authors describe different chromosomal aberrations. In a recent study, Leroux *et al*[44] using conventional cytogenetic and 24-color FISH analyses identified six chromosomal regions frequently affected in these neoplasms. In their series, reproducible loss of chromosomal material occurred on chromosomes 5q, 6q, 9, 12p, 13q, and 15q in 14 of 21 patients. They concluded that there was no single consistent chromosomal aberration, but that a combination or accumulation of certain genomic imbalances might be specific in CD4+CD56+ malignancy.[44]

Treatment outcome

Since there is no consensus for optimal treatment in CD4+CD56+ neoplasms, therapeutic approaches for CD4+CD56+ malignancy vary widely from irradiation in localized stages to myeloablative therapy. Although the initial response rate to treatment is high with almost 70% complete remissions (CR) and 10% partial remissions (PR), only about 20% of patients show a sustained remission at

Table 2 Published cases of CD4+CD56+ malignancies

Authors	*Year*	*n*	*Chemotherapy*	*Irradiation*	*CR/PR*	*Median survival*
Adachi *et al*[10]	1994	1	CHOP	No	0/1	24
Hayashi *et al*[9]	1994	1	CHOP	Yes	1/0	53
Brody *et al*[13]	1995	1	COP	No	0/0	6.5
Nakamura *et al*[14]	1995					
Kobashi *et al*[15]	1996	3	CAMBO-VIP (1), THPOC (1), CHOP+BMT (1)	ND	3/0	17+
Savilo *et al*[16]	1995	1	RT	Yes	1/0	22+
Dummer *et al*[17]	1996	1	IFN-α	Yes+PUVA	0/0	17+
Emile *et al*[18]	1996	2	n.d.	ND	n.d.	4
DiGiuseppe *et al*[19]	1997	4	Prednisone (2), COP+mitoxantrone (1), unknown (1)	No	2/1	8
Savoia *et al*[12]	1997	4	CHOP (1), ACOP-B (1), P-VEBEC (1)	Yes (1)	3/0	8
Drénou *et al*[20]	1997	1	CHOP+MTX, cytarabine, etoposide, allogeneic BMT	TBI	1/0	14+
Uchiyama *et al*[21]	1998	1	IL-2	Yes	1/0	20
Bagot *et al*[22]	1998	1	COP+C	No	1/0	16
Kameoka *et al*[23]	1998	2	CHOP (1), CHOP-like (1)	No	1/0	8
Bastian *et al*[24]	1998	1	No	Yes	1/0	18+
Ko *et al*[25]	1998	1	CHOP	No	1/0	32+
Petrella *et al*[11]	1999	7	COP (1), CP (1), CVBM (1), CCVP (2), DC (1), LDC (1)	No	7/0	17
Mukai *et al*[26]	1999	1	Cis-VACD autoPBSCT	No	1/0	40
Mhawech *et al*[27]	2000	1	CHOP	No	0/1	ND
Nagatani *et al*[28]	2000	4	ACOMP-B (19, COP (1), etoposide, prednisone, IFN-α/γ	Yes (1)	1/2	12.5
Falcão *et al*[29]	2000	3	ALL-regimen (1) CHOP (2)	No	1/0	3
Kojima *et al*[30]	2000	1	Cis-VACD (1)	TBI	2/0	32.5
Ginarte *et al*[31]	2000	1	Cyclophosphamide, vincristine, MTX; i.th. MTX, hydrocortisone, cytarabine	No	1/0	14+
Rakozy *et al*[32]	2001	2	CHOP (1)	No	1/0	17.5
Yamada *et al*[33]	2001	2	Steroids and chemotherapy (1), CHOP (1)	Electron beam therapy (1)	1/1	31
Kimura *et al*[34]	2001	1	ALL-regimen	ND	1/0	13+
Honda *et al*[35]	2001	1	CHOP+sobuzoxane	No	0/1	ND
Alvarez-Larran *et al*[36]	2001	1	CHOP	No	1/0	18
Kato *et al*[37]	2001	1	CHOP+HD Dexa CCE, +autologous PBSCT	No	1/0	13
Aoyama *et al* [38]	2001	1	Vincristine, prednisone	No	1/0	6
Feuillard *et al*[39]	2002	21	Multiple	No	2/17	12
Khoury *et al*[40]	2002	6	CHOP (2), hyper-CVAD (1)+MTX, cytarabine (2), POMP (1)	Yes (1)		7.5
Chen *et al*[41]	2002	1	None	Yes	1/0	ND
Chang *et al*[42]	2002	1	CHOP	Yes	1/0	5+
Bayerl *et al*[43]	2002	3	CHOP (1) CHOP, ifosfamide, etoposide (1), cytarabine, daunorubicin (1)	No	2/0	21+
Petrella *et al*[5]	2002	7	NA (1), DC+RT (1), mini-CEOP (1), ACVBP (1),AVDB (1), CEP (1), HU (1)	No	3/0	8

ACOMP-B: ACOP-B+methotrexate; ACOP-B: doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; ACVBP: daunorubicin, cyclophosphamide, vincristine, bleomycin; prednisone, ALL: acute lymphoblastic leukaemia; AVDB: adriamycin, vincristine, daunorubicin, bleomycin; CAMBO-VIP: cyclophosphamide, doxorubicine, methotrexate, bleomycin, vincristine, etoposide, ifosfamide, prednisone; CCE: carboplatin, cyclophosphamide, etoposide; CEP: cyclophosphamide, eldisine, prednisolone; CHEP: cyclophosphamide, epirubicin, vincristine, prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone; Cis-VACD: cisplatin, vindesine, doxorubicin, cyclophosphamide, dexamethasone; CMi: cytarabine, mitoxantrone; COP: cyclophosphamide, vincristine, prednisone; COP-C: COP+ chlorambucil; CP: chlorambucil, prednisone; CVBM: cyclophosphamide, vindesine, bleomycin, mitoxantrone; DC: daunorubicin, cytarabine; HU: hydroxyurea; Hyper-CVAD: CHOP with hyperfractionated cyclophosphamide; IC: idarubicin, cytarabine; IFN-α: interferon-alpha; IFN-γ: interferon-gamma; IL-2: interleukin-2; i.th.: intrathecal; LAC: lomustine, adriamycin, cytarabine; LDC: DC+lomustine; Mini-CEOP: cyclophosphamide, etoposide, vincristine, prednisone; MTX: methotrexate; POMP: mercaptopurine, vincristine, prednisone; PUVA: psoralen plus ultraviolet A therapy; P-VEBEC: prednisone, vinblastine, epirubicin; bleomycin, etoposide, cyclophosphamide; methotrexate, RT: radiotherapy; THPCOP: cyclophosphamide, THP-doxorubicin, vincristine prednisolone; ND: not determined; CR: complete remission; PR: partial remission.

the last follow-up (median observation 16 months). Most patients relapse and subsequently die of progressive disease. Patients with disease limited to the skin only show a slightly better median overall survival than patients with advanced disease (17 and 12 months, respectively), but the difference is not significant (log-rank test, data not shown). In general, outcome is poor with a median overall survival of 13 months reflecting the aggressive course of the disease (Figure 1). To investigate the impact of different therapies on outcome, treatment of published cases can be separated into four groups according to the intensity of the chemotherapy.

1. *Local therapy or systemic therapy 'less than CHOP'*: Primarily older patients are treated with local therapy or

Table 3 Immunophenotype and EBV diagnostic of CD4+CD56+ malignancies

Pat.	*CD2*	*CD3*	*CD4*	*CD5*	*CD7*	*CD8*	*CD16*	*CD56*	*CD45 RO*	*HLA-DR*	*CD34*	*CD68*	*CD20*	*EBV (LMP)*	*EBER*
Published cases	24/87 28%	0/91 0	90/91 100%	3/83 4%	33/81 40%	1/85 1%	2/71 3%	91/91 100%	4/40 10%	73/78 94%	1/60 2%	23/45 51%	0/70 0	3/18 18%	0/38 0
Own cases	5/5	0/6	6/6	1/6	0/5	0/6	0/1	6/6	1/6	4/4	1/6	5/6	0/5	0/5	0/5
a	–	–	+	–	–	–	ND	+	–	ND	–	–	–	–	–
b	–	–	+	+	–	–	–	+	–	+	–	+	–	–	–
c	–	–	+	–	–	–	ND	+	–	+	–	+	–	–	–
d	–	–	+	–	–	–	ND	+	–	+	+	+	–	–	–
e	–	–	+	–	–	–	ND	+	–	+	–	+	–	–	–
f	ND	–	+	–	ND	–	ND	+	+	ND	–	+	ND	ND	ND

Analysis of surface antigens and EBV-LMP was performed by immunohistochemistry. EBER (Epstein–Barr virus-encoded RNA) was analysed by *in situ* hybridization. ND = not determined.

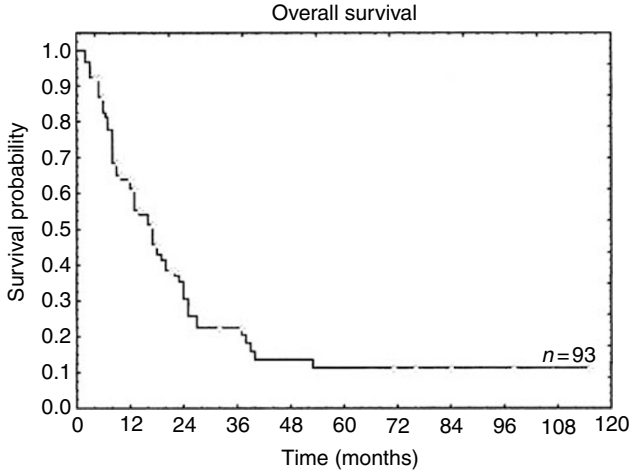

Figure 1 Kaplan–Meier curve of the overall survival for 93 evaluable published and own patients. In four patients follow-up data were missing.

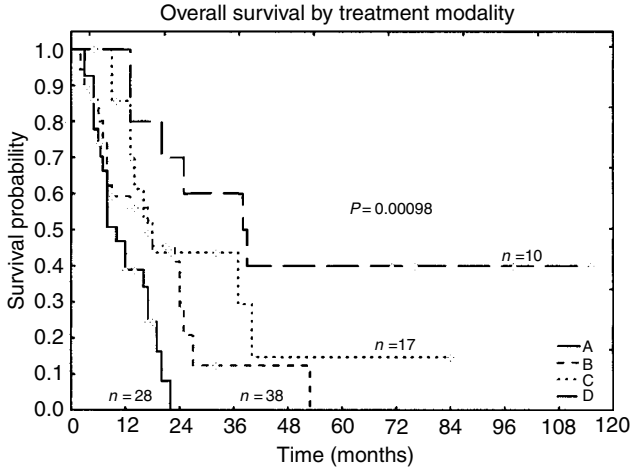

Figure 2 Kaplan–Meier curves of the overall survival for different therapies: A – chemotherapy less intensive than CHOP, including symptomatic therapy and local irradiation; B – CHOP and CHOP-like regimens; C – therapy for acute leukemia; D – autologous or allogeneic stem cell transplantation.

systemic therapy 'less than CHOP'. The median age in this group is 79 years. Chemotherapy regimens were heterogeneous, but mostly cyclophosphamide-based. Some patients only received local radiation ($n=5$), steroid therapy ($n=1$), or supportive care ($n=1$). Despite an overall high response rate of almost 80% (68% CR, 11% PR), this group showed a very poor outcome. Only two authors reported sustained CR (7%) after this therapy; one young patient with skin-restricted disease had radiotherapy; another, a 72-year-old man with widespread disease, was treated with cyclophosphamide, methotrexate, vincristine and intrathecal prophylaxis.[24,31] However, the observation time for the two patients was only 14 and 18 months, respectively. The median overall survival for all evaluable patients is only 9 months and Kaplan–Meier curves do not suggest curative potential for this therapeutic approach (Figure 2). Table 4 summarizes the clinical data for this treatment group (group A).

Table 4 Group A: patients treated with local therapy or systemic therapy 'less than CHOP'

Pat.	*Age/sex*	*Cutaneous manifestations*	*Extracutaneous manifestations*	*Initial therapy*	*CR/PR*	*Survival (months)*
2	63/m	+	+	COP	No	$6^1/_2$
3	47/f	+	–	RT, PUVA, IFN-α	No	17+ (AWD)
4	81/f	+	+	Prednisone	PR	10
5	82/m	+	+	COP + mitoxantrone	CR	8
6	79/m	+	+	Prednisone	CR	3
8	72/m	+	+	RT	No	5
12	89/m	+	–	IL-2, RT	CR	20
15	21/f	+	–	RT	CR	18+
16	86/f	+	+	COP	CR	5
18	67/f	+	–	COP-C	CR	17
19	84/m	+	+	CP	CR	5
20	65/f	+	+	COP-C	CR	17
25	83/m	+	+	COP	No	19
26	89/f	+	+	RT	PR	5
27	82/m	+	+	Etoposide + prednisone + IFNα/γ	CR	8
36	67/f	+	–	COP-C	CR	16
49	76/m	–	+	Symptomatic	No	3
51	81/f	+	+	COP	CR	12
53	69/m	+	+	COP	CR	12
58	79/m	+	–	Cyclophosphamide, etoposide, Prednisone	CR	8
67	67/m	+	+	6-Mercaptopurine, MTX, prednisone	PR	12+
68	70/m	+	+	COP	CR	7
70	79/m	+	+	Vincristine, prednisone	CR	6
77	86/m	+	–	RT	CR	ND
87	64/m	+	+	CEP	CR	6+ (PD)
88	88/f	+	–	HU	No	8
89	72/m	+	+	Cyclophosphamide, MTX, vincristine + i.th.	CR	14+
90	81/m	+	–	RT	CR	22+ (AWD)
$n=28$	Med. 79 m:f 18:10	27/28 96%	19/28 68%		19CR 68% 3PR 11%	Med. OS 9 CR at last follow-up 2/28 (7%)

AWD: alive with disease; CEP: cyclophosphamide, eldisine, prednisolone; COP: cyclophosphamide, vincristine, prednisone; COP-C: COP + chlorambucil; HU: hydroxyurea; IFN-α: interferon-alpha; IFN-γ: interferon-gamma; IL-2: interleukin-2; i.th: intrathecal; MTX: methotrexate; PUVA: psoralen plus ultraviolet A therapy; RT: radiotherapy; CR: complete remission; PR: partial remission; ND: not determined.

2. *CHOP and CHOP-like regimens*: CHOP/CHOP-like chemotherapy was used most frequently in CD4+CD56+ malignancies (group B). However, compared to less aggressive therapies (group A) this moderately intensive treatment did not result in better response rates or survival benefit. The overall response rate in almost 40 evaluable patients was about 70% (55% CR), but sustained CR was only observed in one patient within this treatment group (Table 5) with a short follow-up of only 4 months.[39] Taken together, CHOP (-like) therapy, like less aggressive treatments, did not seem to provide curative potential.

3. *Intensive acute leukemia protocols*: Since CD4+CD56+ neoplasms usually show an aggressive course with frequent bone marrow involvement, intensive treatment according to acute leukemia seems an appropriate therapeutic approach (group C). Different protocols were investigated with a high CR rate of 94%. Sustained CR can be achieved with these regimens in about one-third of patients. Although median observation time for these responders was only 7.5 months, Falcão *et al*[29] reported a young boy continuing in CR for seven years following therapy for acute lymphoblastic leukaemia. Table 6 shows the data for this treatment group.

4. *Myeloablative therapy*: Experience with myeloablative therapy in CD4+CD56+ malignancy is limited to 10 patients (four autologous and six allogeneic transplants) that are summarized in Table 7. All patients in whom data on myeloablative therapy were evaluable underwent total body irradiation and all but one received high-dose cyclophosphamide (alone or in combination with other chemotherapeutic agents). The entire group (group D) had a median survival of 31.5 months. However, only two of the six patients receiving allogeneic transplant relapsed (median overall survival 38.5 months) compared to three relapses in the four patients with autologous transplant (median survival 16.5 months). Autologous peripheral blood stem cell transplantation (APBSCT) with one exception did not lead to long-lasting disease-free survival. However, in the allogeneic setting, all but one patient remained disease-free, if the transplantation has been performed in first remission. However, this treatment is restricted to younger patients as reflected by the median age of 28.5 years in this group.

Taken together, overall response rate (CR and PR after initial therapy) is high regardless of therapy and does not show pronounced differences in the four groups. On the

Table 5 Group B: patients treated with CHOP or CHOP-like regimens

Pat.	*Age/sex*	*Cutaneous manifestations*	*Extracutaneous manifestations*	*Initial therapy*	*CR/PR*	*Survival (months)*
1	67/m	+	+	CHOP	PR	24
9	78/m	+	+	ACOP-B	CR	8
10	72/m	+	–	CHOP	CR	17 + (AWD)
11	60/m	+	+	P-VEBEC	CR	11
13	21/f	+	+	CHOP-14	CR	14 + relapse
14	81/m	+	+	CHOP-like	ND	2
17	38/m	+	–	CVBM	CR	27
24	71/m	+	+	ACOMP-B	PR	17
28	18/m	–	+	CHOP	CR	32 + relapse
31	18/m	+	+	CHOP	No	2
32	68/m	+	+	CHOP-bleomycin	No	3
33	57/m	+	+	CAMBO-VIP	CR	32 + relapse
34	78/m	+	+	CHOP	CR	9 + relapse
37	47/m	+	–	CHOP	ND	5
40	67/m	+	+	Electron beam + CHOP	PR	25
42	65/m	–	+	CHOP + sobuzoxane	PR	+
44	55/m	+	+	Cis-VACD	CR	25
47	53/m	–	+	CHOP + RT	CR	53
48	45/f	–	+	CHOP	PR	+
54	75/m	–	+	Etoposide, cytarabine, ifosfamide	CR	6
55	72/m	+	+	CHEP	PR	23
60	74/m	+	–	Etoposide, ifosfamide	CR	17
63	75/f	+	+	Cyclophosphamide, vincristine, prednisone, daunorubicin	No	9
65	82/m	+	+	CHOP without prednisone	CR	4 +
71	56/m	+	+	Hyper-CVAD	CR	24
72	61/m	+	+	Hyper-CVAD	ND	6
73	73/m	+	+	Hyper-CVAD, MTX, cytarabine	CR	24
74	52/m	+	+	Hyper-CVAD, MTX, cytarabine	CR	3
75	85/f	+	+	CHOP + RT	No	7
76	77/m	+	+	CHOP	No	8
78	19/f	+	–	CHOP	CR	5 + AWD
79	71/m	+	+	CHOP	CR	21 + (SD)
81	66/m	+	–	CHOP	No	13
84	72/m	+	+	Mini-CEOP	No	3
85	33/f	+	+	ACVBP	CR	27
86	77/m	+	–	AVDB	No	7
91	73/m	+	+	CHOP	CR	18
c	74/f	+	+	Vincristine, prednisone, CHOP	CR	8
n = 38	Med. 67.5 m:f 31:7	34/38 89%	31/38 82%		21CR 55% 6PR 16%	Med. OS 13 CR at last follow-up 1/38 (3%)

ACOMP-B: ACOP-B + methotrexate; ACOP-B: doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; ACVBP: daunorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; AVDB: adriamycin, vincristine, daunorubicin, bleomycin; CAMBO-VIP: Cyclophosphamide, doxorubicine, methotrexate, bleomycin, vincristine, etoposide, ifosfamide, prednisone; CHEP: cyclophosphamide, epirubicin, vincristine, prednisone; CHOP: cyclophosphamide, vincristine, doxorubicin, prednisone; Cis-VACD: cisplatin, vindesine, doxorubicin, cyclophosphamide, dexamethasone; CVBM: cyclophosphamide, vindesine, bleomycinn, mitoxantrone; Hyper-CVAD: CHOP with hyperfractionated cyclophosphamide; Mini-CEOP: cyclophosphamide, etoposide, vincristine, prednisone; MTX: methotrexate; P-VEBEC: prednisone, vinblastine, epirubicin, bleomycin, etoposide, cyclophosphamide; RT: radiotherapy; CR: complete remission; PR: partial remission; ND: not determined.

other hand, maintenance of CR is better, with more aggressive treatment (group A: 7%, group B: 3%, group C: 35%, and group D: 50%, respectively). Figure 2 shows Kaplan–Meier survival curves for the different treatment groups. The overall survival between groups C and D was significantly higher than in groups A and B. Group D alone was also significantly superior to groups A, B, and C. However, age $\geqslant$60 years was a negative prognostic factor in CD4 + CD56 + neoplasms that strongly influences outcome (Figure 3) and median age decreased when more intensified therapy was provided: 79 years (group A), 67.5 years (group B), 52 years (group C), and 28.5 years (group D), respectively. Elderly patients survived for a median of 9 months (range 2–40 months) compared to younger patients with a significantly longer median survival of 18 months (range 2–84 months; $P<0.0001$). Older age in less aggressive treatment groups might at least partly explain poor outcome. Therefore, we performed an age-adjusted evaluation that revealed significant superiority in the overall survival only for allogeneic stem cell transplantation in the first remission (Figure 4).

Conclusions

CD4 + CD56 + neoplasms are a distinct entity with a characteristic CD4 + CD56 + CD3-phenotype, usually with rapid and aggressive course and poor outcome. Since skin-

Table 6 Group C: patients treated with an intensive acute leukemia protocol

Pat.	*Age/sex*	*Cutaneous manifestations*	*Extracutaneous manifestations*	*Initial therapy*	*CR/PR*	*Survival (months)*
21	49/f	+	+	DC	CR	9
22	37/m	+	–	LDC	CR	32+ (AWD)
30	8/m	+	+	Brazilian ALL-regimen (GTBLI-93)	CR	84+
41	34/m	+	+	JALSG ALL87 regimen	CR	13+
50	8/m	+	+	CMi	CR	37
52	68/f	+	+	LAC	CR	22
57	55/m	+	+	LAC	CR	16
59	14/m	+	+	Vincristine, prednisone, daunorubicin, asparaginase	CR	10+
61	74/f	+	+	Vincristine, 6-mercaptopurine, cyclophosphamide, cytarabine	CR	5+
62	67/m	+	+	IC	CR	5+
64	60/m	+	+	LAC	CR	9
66	56/m	+	+	DC	CR	13
82	8/m	+	+	CMi	CR	33
83	62/m	+	–	DC+RT	No	13
a	60/m	+	+	Vincristine, daunorubicin, prednisone, HAM	CR	40
b	71/m	+	+	DA, ETI	CR	18
f	67/f	+	–	DA	CR	4+ (under therapy)
n=17	Med. 56 m:f 13:4	14/14	14/17 82%		16CR 94%	Med. OS 13 CR at last follow-up 6/17 (35%)

ALL: acute lymphoblastic leukemia; AWD: alive with disease; CMi: cytarabine, mitoxantrone; DA: daunoblastin, cytarabine; DC: daunorubicin, cytarabine; ETI: etoposide, thioguanin, idarubicin; HAM: high-dose cytarabine, mitoxantrone; IC: idarubicine, cytarabine; JALSG: Japan Adult Leukemia Study Group; LAC: lomustine, adriamycin, cytarabine; LDC: DC+lomustine; RT: radiotherapy; CR: complete remission; PR: partial remission.

Table 7 Group D: patients treated with myeloablative protocols

Pat.	*Age/sex*	*Cut. manif.*	*Extracut. manif.*	*High-dose chemotherapy±TBI*	*Source of stem cells*	*BM/peripheral*	*Time of Tx*	*Survival (months)*
29	29/m	–	+	HD cyclophosphamide +TBI	Allogeneic	BM	First CR	76+ in CR
35	24/f	+	+	HD cyclophosphamide melphalan+TBI*	Allogeneic	BM	First CR	115+ in CR*
38	35/m	+	–	ND	Allogeneic	BM	Second CR	39 died of sepsis in PD
56	6/f	–	+	Aracytidine, melphalane+TBI*	Allogeneic	BM	First CR	98+ in CR
69	28/m	+	–	HD cyclophosphamide + TBI*	Allogeneic	BM	First CR	38 AWD relapse at 12 months
80	29/m	+	–	ND	Allogeneic	BM	Third CR	25 died in CR due to ARDS
d	23/m	+	+	Busulfan, thiotepa, fludarabine, ATG − TBI	Allogeneic	Peripheral	Second CR	20 died in CR therapy-related
23	25/m	+	+	HD cyclophosphamide, etoposide+TBI	Autologous	Peripheral	PR after First relapse	71+ in CR*
43	51/m	+	+	HD cyclophosphamide, carboplatin, etoposide, dexamethasone − TBI*	Autologous	Peripheral	First CR	13 PD died of pneumonia
d	23/m	+	+	HD cyclophosphamide +TBI	Autologous	Peripheral	First CR	20 relapse see above
e	32/m	+	+	HD cyclophosphamide +TBI	Autologus	Peripheral	First CR	13 DOD
n=10	Med. 28.5 m:f 8:2	8/10 80%	7/10 70%		allo:auto 7:4**	BM/ peripheral 6:5**		Med. OS 31.5 CR at last follow-up 5/10 (50%)

*Personal communication.
**Patient d underwent both autologous and allogeneic stem cell transplantion.
Cut. manif: cutaneous manifestations; extracut. manif.=extracutaneous manifestations; ARDS: acute respiratory distress syndrome; ATG: antithymocyte globulin; AWD: alive with disease; BM: bone marrow; DOD: died of disease; HD: high dose; TBI: total body irradiation; Tx: transplantation; CR: complete remission; PR: partial remission; PD: progressive disease; ND: not determined.

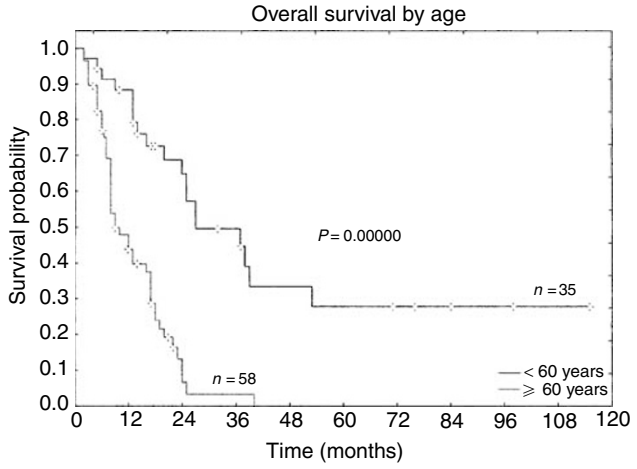

Figure 3 Kaplan–Meier curves of the overall survival according to age (including all treatment groups).

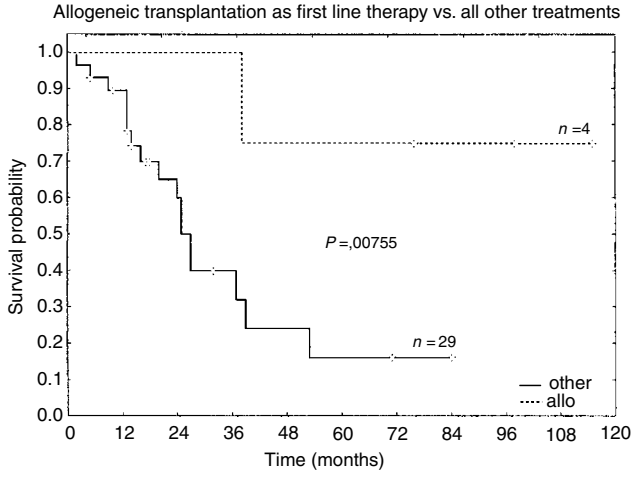

Figure 4 Kaplan–Meier curves of the overall survival for patients <60 years showing survival benefit for allogeneic transplantation.

restricted disease shows no better outcome than primarily disseminated disease, CD4+CD56+ neoplasms must be considered as a primarily systemic disease. Despite initial good response to various (chemo-) therapies, median overall survival is only 13 months and therapeutic guidelines are not yet defined, mainly because of its rare occurrence.

Treatment that is more aggressive than the CHOP regimen (groups C and D) results in better response rates compared to less intensive therapies (groups A and B). While intensive therapy for acute leukemia (group C) only enhances the rate of sustained CR, myeloablative treatment (group D) also leads to a marked increase of median survival of 38.5 months. However, age ⩾60 years is a negative prognostic factor, which is consistent with findings in malignant lymphoma and myeloid malignancies. In an age-adjusted evaluation only allogeneic stem cell transplantation in first CR showed significant superiority in terms of the overall survival compared to all other treatments in

Table 8 Clinical features of own cases

Pat.	*Age/sex*	*Cutaneous lesions*	*Extracutaneous manifestations*	*Genetics**	*Initial treatment*	*Response*	*Site of relapse*	*Salvage therapy*	*Outcome (months)*
a	60/m	Thorax	BM, LN, nasopharynx	mos46,XY/45,XY, t(12;15) (p11;q11)	Vincristine, daunorubicin, prednisolone, HAM	CR	BM	ICE	40 DOD
b	71/m	Trunk	BM, leukemia, LN	46, XY	DA, ETI	CR	Skin, BM	Cytarabine, CHOP, FC	18 DOD
c	74/w	Scalp, trunk, upper arms	BM, leukemia	mos46,XX/44,XX,-9	CHOP	CR	BM, leukemia, spleen	Palliative	8 DOD
d	23/m	Diffuse	BM	46, XY	CHOP, MTX (i.th.) autologous PBSCT	CR	Skin, BM, LN, CNS, spleen	ESHAR allo-TX	20 in CR d+52 therapy related
e	32/m	Face, lower legs	BM, leukemia LN, CNS	rev ish dim 5q21-q32 rev ish dim 9 rev ish dim 13q rev ish enh 14q32	CHOP, MTX (i.th.) autologous PBSCT	CR	Skin, BM, leukemia, LN, CNS,	T-ALL regimen	13 DOD
f	67/f	Mamma	No	ND	DA	CR			4+ under therapy

*In all cases except case e, classical cytogenetics was performed. Case e was investigated by comparative genomic hybidization.
ALL: acute lymphoblastic leukemia; ATG: antithymocyte globulin; BM: bone marrow; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CNS: central nervous system; DA: daunorubicin, cytarabine; DOD: died of disease; ESHAP: etoposide, methylprednisone, cytarabine, cisplatin; ETI: idarubicine, thioguanine, etoposide; FC: fludarabine, cyclophosphamide; HAM: high-dose cytarabine, mitoxantrone; ICE: idarubicin, cytarabine, etoposide; i.th: intrathecal; LN: lymph nodes; MTX: methotrexate; CR: complete remission.

patients <60 years. Since allogeneic stem cell therapy is limited to younger patients and most patients with CD4+CD56+ malignancy are in their seventh decade of life, the vast majority of patients are not eligible for this otherwise promising therapeutic option.

Our own experience confirms the above results (Table 8). Patients initially were treated either with CHOP or combination chemotherapy designed for acute leukemia. All patients died with a median survival of 15.5 months including one patient who underwent autologous PBSCT in the first remission. Another patient who relapsed after autologous PBSCT achieved a second CR following allogeneic peripheral stem cell transplantation, but died as a complication of treatment on day +52. To our knowledge, this is the first patient with CD4+CD56+ malignancy who received peripheral allogeneic stem cell transplantation and who underwent both autologous and allogeneic stem cell transplantation.

In summary, allogeneic stem cell transplantation in the first CR should be recommended for younger patients with CD4+CD56+ neoplasms with curative intent. For patients not eligible for allogeneic stem cell transplantation, the best therapy still is unknown. Owing to a high early relapse rate, we would not recommend autologous PBSCT for these patients. Whether nonmyeloablative therapy followed by allogeneic transplantation or maintenance therapy will improve outcome remains to be evaluated.

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