Nonpegylated liposomal doxorubicin is highly active in patients with B and T/NK cell lymphomas with cardiac comorbidity or higher age

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ORIGINAL ARTICLE

Nonpegylated liposomal doxorubicin is highly active in patients with B and T/NK cell lymphomas with cardiac comorbidity or higher age

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Abstract We used nonpegylated liposomal doxorubicin (NPLD) in cytostatic drug combinations to treat 37 patients with non-Hodgkin's lymphoma and pre-existing cardiac disorder or elderly patients with reduced physical state who were ineligible for conventional anthracycline-containing therapy. High remission rates were observed in this poor-risk population: Complete remission rates were 75% for diffuse large B cell lymphoma (DLBCL) and 55% for T/NK cell neoplasm (overall response rate of 80% and 89%, respectively). Twenty-seven patients (73%) are still alive after a median observation time of 14 months. No major cardiac or gastrointestinal toxicity was observed. Extravasation of NPLD in two patients resulted in mild inflammation without tissue damage. Hematologic toxicity was comparable to that of conventional anthracycline-containing regimens. We conclude that NPLD is highly active in combination chemotherapy for lymphoma with low cardiac toxicity in patients with pre-existing cardiac disorders or higher age. Moreover, we also observed remarkable efficacy in T/NK cell lymphomas.

Keywords Non-Hodgkin's lymphomas · Nonpegylated liposomal doxorubicin · Efficacy · Cardiac comorbidity · Older age

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Introduction

Anthracycline-based chemotherapy is effective in the treatment of patients with non-Hodgkin's lymphoma (NHL) [1–6] and superior to other drugs in controlling disease in young as well as in elderly patients. However, elderly patients often have considerable comorbidity, especially of the cardiovascular system, and are treated with other drug combinations to avoid anthracycline-induced cardiotoxicity [7–13]. On the other hand, the incidence of aggressive lymphomas in the elderly is increasing.

Cardiotoxicity is probably caused by free radicals generating myofibril loss and peroxidation of the cardiomyocyte plasma membrane [14].

The risk of doxorubicin-induced congestive heart failure (CHF) increases with cumulative dose [15] because of a low proliferation rate of cardiomyocytes. Other risk factors are patient's age [15–17], a history of coronary heart disease, valvular heart disease, hypertension, diabetes, cigarette smoking, or obesity. In multivariate analysis,

doxorubicin use was significantly associated with an increased risk of subsequent CHF in a recent study [18]. Hypertension and diabetes were additional independent risk factors for the development of CHF in patients treated with doxorubicin [18].

CHF induced by anthracycline-based chemotherapy seems to have a worse prognosis than idiopathic CHF [19].

Therefore, a number of therapy modifications have been published. As patients receiving less than six treatments had no increased risk of CHF, a reduction of treatment cycles containing doxorubicin could be considered. However, among patients aged 60 to 74 years, early termination was associated with worse survival, but among patients older than 74 years, it was not [20].

Another option, the replacement of doxorubicin by epirubicin does not protect from cardiotoxicity [21]. The addition of cardioprotective drugs such as dexrazoxane increases myelotoxicity [22] and thus probably results in limited treatment efficacy [23]. Also, the CNOP protocol with mitoxantrone substituting doxorubicin was significantly inferior to cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP) regarding response rate and slightly inferior overall survival [24].

Another published approach is the use of angiotensin II receptor blockers in NHL patients receiving doxorubicin-based therapy [25].

Liposomal doxorubicin in its pegylated form has been evaluated in elderly patients with aggressive lymphomas. The liposomal formulation leads to reduced organ toxicity (including cardiotoxicity), without reducing activity in tumor cells, and similar complete response rates compared to treatment with doxorubicin in a standard formulation [26, 27].

The liposome-encapsulated doxorubicin administered in this study is a nonpegylated form and protects from the accumulation of doxorubicin in skin and mucosa ("hand-and-foot-syndrome") [28].

To date, there are few reports about the efficacy of nonpegylated liposomal doxorubicin (NPLD) in patients with malignant lymphoma [28]. Recently, NPLD in combination with rituximab, cyclophosphamide, vincristine, and prednisone (R-COMP) has been shown to be effective with a low cardiotoxicity profile in 21 patients with diffuse large B cell lymphoma (DLBCL) [29]. Another study including 20 patients with aggressive lymphoma showed a complete response rate of 65% and a partial response (PR) rate of 25% in frail patients treated with R-COMP [30].

T cell and NK cell neoplasms are a heterogeneous group of NHL characterized usually with an aggressive clinical course [31]. Overall response (OR) to CHOP or CHOP-like protocols in T/NK cell neoplasms is inferior when compared with B cell neoplasms. In other than anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL), this regimen has low efficacy [31].

Prognosis is dependent on histological subtype, the International Prognostic Index, or other markers such as the presence of detectable T cell receptor rearrangements [32, 33].

In addition, it has been shown that the use of anthracyclines does not prolong survival in peripheral T cell lymphoma, not otherwise specified (PTCL, NOS) [34]. Therefore, new combinations or dose-intensified approaches have been explored. High-dose therapy with autologous stem cell transplantation as consolidation after first complete remission (CR) seems to be promising, but most of the studies are retrospective [35]. Unfortunately, these strategies cannot be used in elderly patients with a reduced physical health state.

In a pilot study comparing CHOP with more intensive regimen (hyper-CAVD; cyclophosphamide, mesna, doxorubicin, vincristine, prednisone, methotrexate, cytarabine), a higher response has been shown in patients receiving pegylated doxorubicin HCl liposome injection (HCVID DOXIL) instead of doxorubicin [36]. However, the CR rate was similar to previous studies using other therapeutic agents.

Here, we report the use of NPLD in combination chemotherapy in 37 patients with lymphoma with cardiac comorbidity and/or higher age. For the first time, the efficacy of NPLD as a part of standard therapy regimen (COMP) in T/NK cell lymphomas will be shown.

Patients and methods

Patients

A total number of 37 patients were included in the present retrospective study. The median age was 73 years (range 37–88 years).

The following entities were included (according to the World Health Organization 2008 classification [37]): 20 DLBCL, nine T/NK cell neoplasms (two angioimmunoblastic T cell lymphomas [AITL], two ALCL (ALK status not known), three PTCL, NOS, and two blastic NK cell lymphomas, now known as blastic plasmacytoid dendritic cell neoplasm), three follicular lymphomas (FL), two post-transplant lymphoproliferative disease (PTLD), two chronic lymphocytic leukemias (CLL), and one multiple myeloma (MM).

The median age of the 20 DLBCL patients was 74 years (range 37–88 years). In 75% (N=15), NPLD was given as first-line therapy; in 15% (N=3), as second-line therapy; and in 10% (N=2), as third-line therapy.

The median age of patients with NK/T cell neoplasm was 74 years (range 64–80 years). In all of these patients, NPLD was given as first-line therapy.

Therapy

Reasons for the use of NPLD were: higher age (N=13; median age 79 years), pre-existing cardiac disorders (N=16), previous therapy with anthracyclines (N=3), or reduced physical health state (N=5). Of the 13 elderly patients, five were in additional reduced general condition, one had a chronic obstructive pulmonary disease, and one had elevated B-type natriuretic peptide (BNP) levels. Pre-existing cardiac disorders included status post myocardial infarction, cardiomyopathy, reduced left ventricular ejection fraction (N=6), elevated BNP levels (N=10, median 680 pg/ml), status post heart transplantation, and status post aortic valve replacement.

Of all 37 patients, 29 (78%) were previously untreated. The following combination regimens were given: R-COMP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, vincristine 2 mg, NPLD 50 mg/m^2, prednisone; thrice weekly; N=25), COMP (cyclophosphamide 750 mg/m^2, vincristine 2 mg, NPLD 50 mg/m^2, prednisone; thrice weekly; N=11), and BMD (bortezomib, NPLD, dexamethasone; N=1). The median number of NPLD containing cycles administered per patient was five (range two to eight).

Two patients received additional intrathecal therapy. One patient with DLBCL received three cycles of liposomal cytarabine intrathecal, and one patient with testicular DLBCL received three cycles of liposomal cytarabine and one cycle of methotrexate intrathecal.

For various reasons, NPLD was reduced to a dose of less than 50 mg/m^2 in 20 patients. The median age of patients who received a reduced dose was 76 years; the median age of patients without dose reduction was 70 years. Of the 20 patients with dose reduction, nine had DLBCL, five had NK/T cell neoplasm, two had CLL, two had FL, and two had PTLD. In the other group (without dose reduction), ten had DLBCL, four had NK/T cell neoplasm, one had FL, and one had MM. In one patient, complete information on NPLD dose was not available. In the group with reduced dose, NPLD combinations were given as first-line therapy in 12 patients (63%), while in the other group, NPLD combinations were given as first-line therapy in all but one patient (94%). The median number of NPLD containing cycles was four in the group with dose reduction and five in the other group.

In 20 patients, supportive therapy with granulocyte colony-stimulating factor (G-CSF) was given. Of these, ten patients had a reduced NPLD dose and ten had no dose reduction.

Response evaluation was performed according to international guidelines [38].

Statistical analysis

Statistical analysis (Kaplan–Meier survival analysis) was performed using WinSTAT© Version 3.0.

Results

Efficacy in diffuse large B cell lymphoma

Patients with DLBCL were treated with R-COMP. CR rate was 75% (15 out of 20; Table 1). One patient had a PR and four had no response (NR). After a median follow-up of 14 months, 15 patients are still alive (75%; Fig. 1). All 15 patients with a CR are still alive, while the four NR patients and the patient with PR have died.

Efficacy in T/NK cell neoplasm

Patients with T/NK cell neoplasm were treated with COMP. Five patients with T/NK cell neoplasm had a CR (56%), three had a PR (33%), and one had an early relapse. Therefore, the OR rate was 89% (Table 1). To date, four patients of this group died, three after a PR and one after early relapse.

In detail, both patients with AITL and both patients with ALCL had a CR. Of three patients with PTCL, NOS, two had PR and one had CR. Of the two blastic NK cell lymphomas (blastic plasmacytoid dendritic cell neoplasms), one had PR and one had early relapse. The OR in AITL, ALCL, and PTCL, NOS was 100% (Table 1).

Overall survival analysis for patients with DLBCL treated with R-COMP and T/NK cell neoplasms treated with COMP showed no significant difference between these entities (Fig. 1).

Efficacy in other hematological malignancies

Of three FL patients with R-COMP, two had a CR and one a PR. The two patients with CR are still alive, while the patient with PR died. The patients with a CR had NPLD as first-line therapy, while in the patient with a PR, NPLD was used as second-line therapy. Therefore, the CR rate for a first-line therapy in FL patients was 100%.

CLL patients were treated with R-COMP. One CLL patient had stable disease (SD), and one did not respond. Both patients are still alive. The patient with SD had NPLD as a third-line therapy, while the patient who did not response had NPLD as a second-line therapy.

Table 1 Clinical outcome in patients with different hematological malignancies treated with NPLD-containing regimens

	OR (%)	CR (%)	PR (%)	NR (%)	ER (%)
DLBCL	80	75	5	20	–
T/NK cell neoplasms	89	56	33	–	11
PTCL, NOS	100	33	67	–	–
ALCL	100	100	–	–	–
AITL	100	100	–	–	–
NK	50	–	50	–	50

OR overall response, *CR* complete remission, *PR* partial response, *NR* no response, *ER* early relapse

Of two PTLD patients treated with COMP, one had a CR and one had a PR. Both patients are still alive.

The myeloma patient had BMD as first-line treatment and reached PR.

Efficacy and dose reduction

Of 20 patients with reduced NPLD dose (R-COMP in 13 patients, COMP in seven patients), 12 (60%) had a CR, and four (20%) had a PR. The OR was 80% in this group. One patient had SD, and three did not respond (15%). All three nonresponders and two of the PR patients died. All patients who did not respond in this group had DLBCL.

In the group without dose reduction, 69% (11 out of 16) had a CR and 19% (three out of 16) had a PR (OR=88%). Only one patient did not respond and died after follow-up. This patient had a DLBCL.

Overall survival analysis for patients with and without dose reduction showed no significant difference (Fig. 2).

Cardiac toxicity

No major cardiac toxicity was observed. In patients with cardiac disorders (N=16), the median BNP level was 938.5 pg/ml (range 346.7–4,845.0 pg/ml; normal range 0–125 pg/ml), while in the other patients, the median BNP level was 187.1 pg/ml (range 62.9–810.8 pg/ml).

In six patients of our cohort, BNP levels before and after NPLD-containing therapy were available (Fig. 3). Median BNP levels were 407.7 pg/ml (range 62.9–2,098.0 pg/ml) before and 514.3 pg/ml (range 53.4–1,212.0 pg/ml) after NPLD-containing therapy (Fig. 3). No major increase of BNP was observed in most patients. In one patient, BNP level even decreased from 2,098 pg/ml before to 330.7 pg/ml after therapy. This patient had DLBCL and received R-COMP as a first-line therapy. The patient had a CR and is still alive after a follow-up of 14 months.

No cardiac event in any patient during or after therapy with NPLD was observed.

Hematologic toxicity

Hematologic toxicity was comparable to that of conventional anthracycline-containing regimens: CTC grade 3 or 4 toxicity for leucopenia/neutropenia occurred in 22 patients (59% of all patients, 82% of patients with DLBCL, and 56% of patients with T/NK cell neoplasm; Table 2).

In the patient group without dose reduction, the percentage of grade 3 or 4 hematologic toxicity was 79% (11 out of 14), while in patients with dose reduction, hematological toxicity occurred in 65% (11 out of 17; Table 2).

Twenty patients (54%) received G-CSF for primary or secondary prophylaxis in at least one cycle of treatment.

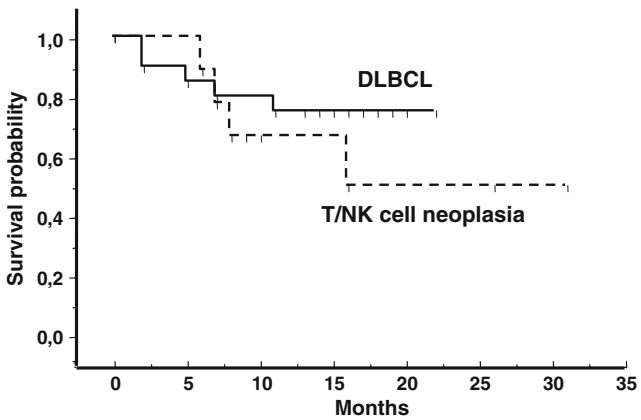

Fig. 1 Overall survival of patients with DLBCL treated with R-COMP (N=20) and patients with NK/T cell neoplasia treated with COMP (N=9)

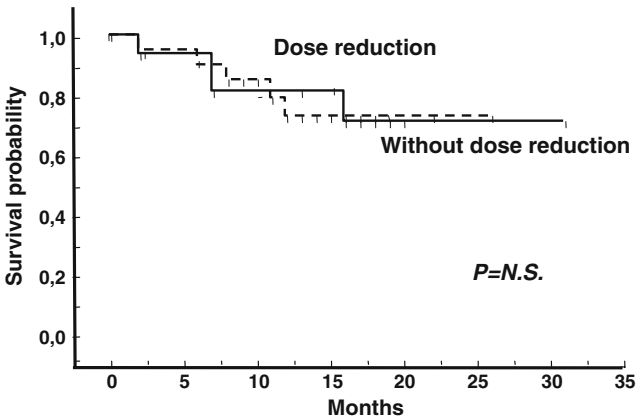

Fig. 2 Overall survival of all patients with (N=20) and without (N=16) dose reduction of NPLD. Median survival is not reached in both groups

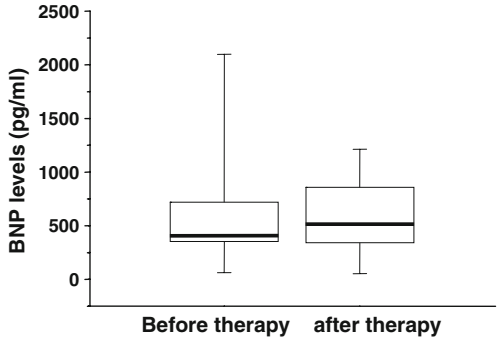

Fig. 3 BNP levels measured before and after NPLD-containing therapies in six patients. Median BNP levels were 407.7 pg/ml (range 62.9–2,098.0 pg/ml) before and 514.3 pg/ml (range 53.4–1,212.0 pg/ml) after NPLD-containing therapy

Nonhematologic toxicity

No gastrointestinal toxicity was observed. Of note, extravasation of NPLD occurred in two patients, but resulted in mild inflammation only, without major tissue damage.

Discussion

We show that NPLD-containing chemotherapy regimens were effective in 20 patients with DLBCL, and our data confirm two previous studies including 20 and 21 patients, respectively. In addition, efficacy was also shown in T/NK cell neoplasms. There are only two reports about the use of pegylated liposomal doxorubicin in this entity. One report mainly including patients with DLBCL showed only poor outcome in a small subgroup with aggressive T cell lymphoma [28, 39]. This study included younger patients with a median age of 55 years. In another report, liposomal doxorubicin was used as a part of an intensive treatment regimen [35]. In this subgroup, a high OR rate has been shown, possibly indicating higher efficacy of liposomal doxorubicin in T/NK cell neoplasms. However, this data still needs further follow-up. Such intensive multidrug regimen may not be suitable for our patient cohort including elderly patients, patients with a reduced general condition, or patients with cardiac morbidity. Efficacy of NPLD has not been reported as a part of a standard chemotherapy regimen including elderly or frail patients, until now. However, in our study, COMP has been effective and safe in nine patients with NK/T cell neoplasms at a median age of 74 years. This is a novel finding. Of note, in three patients with PTCL, NOS, which represents a high-risk group, a response to NPLD-containing treatment was observed.

In our cohort, in patients with NK/T cell neoplasms, no significant difference regarding overall survival compared to patients with DLBCL was found (Fig. 1).

We analyzed the impact of dose reduction of therapy with R-COMP and COMP on OR rates. In our study, there was only little difference regarding OR rate in patients with or without reduced dose (80% vs. 88% respectively). This data showed that NPLD could also be effective with a reduced dose. On the other hand, full-dose NPLD did not promote a significantly higher toxicity, so that NPLD could be used in full dose also in elderly patients or patients with comorbidities. No difference was observed regarding overall survival (Fig. 2).

Importantly, nonhematologic toxicity was mild in our study. There was no gastrointestinal toxicity observed.

None of the patients had a cardiac event during or after NPLD-containing regimen. Moreover, no significant cardiac toxicity was observed in our patient cohort when using BNP levels as a marker for cardiac dysfunction. We showed BNP levels in six patients before and after therapy.

NPLD is known to be cardioprotective when compared with doxorubicin. Echocardiography has been used to determine cardiac function before treatment with NPLD [29, 40]. BNP as marker for cardiac dysfunction could be used for therapeutic monitoring [41–43]. However, BNP levels can currently not be used instead of echocardiography and the predictive value of BNP elevations remains uncertain [44, 45]. Natriuretic peptides may be associated with impairment of left ventricular diastolic filling in the development of doxorubicin-induced cardiac dysfunction [46]. We analyzed BNP levels before and after therapy. In only one of our selected patients, a major increase of BNP could be observed. However, the use of BNP as a follow-up marker should be analyzed in larger patient cohorts receiving NPLD-containing therapy.

Anthracycline-based therapy is also characterized by the risk of extravasation with severe tissue necrosis [47]. Interestingly, in two patients, extravasation occurred and resulted only in a mild inflammation. This is another advantage of therapy with NPLD compared with doxorubicin.

Hematologic toxicity corresponded to that of conventional anthracycline-containing regimens. However, the use of G-CSF according to international guidelines is recommended to avoid fatal infectious complications.

Table 2 Hematological toxicity of NPLD-containing therapy

	Hematological toxicity grade III–IV (%)	Hematological toxicity grade I–II (%)
DLBCL	82	12
T/NK cell neoplasms	56	33
Dose reduction	65	24
Without dose reduction	79	14

We conclude that NPLD is highly active in combination chemotherapy for B cell lymphomas with low incidence of cardiac toxicity in patients with pre-existing cardiac disorders or higher age. Moreover, we herewith report high efficacy in T/NK cell neoplasms representing a high-risk population. This data warrants investigation in large clinical trials. A randomized study evaluating cardiac effects of substitution of conventional doxorubicin by NPLD in combination chemotherapy (R-CHOP vs. R-COMP) is currently being conducted by the Austrian Cooperative Group on Cancer Drug Therapy (AGMT).

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