A retrospective analysis of combination chemotherapy consisting of cyclophosphamide, vincristine, prednisolone and procarbazine (C-MOPP) for pretreated aggressive non-Hodgkin lymphoma.

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Abstract

The C-MOPP regimen, consisting of cyclophosphamide, vincristine, prednisolone and procarbazine, has been used for treatment of non-Hodgkin lymphoma; however, there are few reports of this therapy against aggressive lymphoma. We performed a retrospective analysis of previously treated 89 patients who had received C-MOPP therapy from 1999 to 2013 at our institution. Median age was 67 (range, 22ï 81) years. Twenty-eight patients obtained CR, 5 obtained PR, and overall response rate was 37% (33/89). The estimated 1-year overall survival and progression-free survival rates were 61% and 33%, respectively. Major grade >2 toxicities were leukopenia (55%) and neutropenia (52%). Efficacy and toxicity was in line with other recent studies involving new agents, given that the subjects mainly consisted of elderly outpatients. These data provide a rationale for the use of C-MOPP as a current control treatment arm when the response to new cancer therapy agents is evaluated.

Key words: Non-Hodgkin lymphoma; Refractory; Relapsed; Salvage therapy; Palliative chemotherapy

Introduction

For relapsed or refractory aggressive lymphoma, high-dose chemotherapy or clinical trials are recommended.[1-2] However, a significant number of patients have no indication for these therapies because of their age, comorbidities or chemotherapy resistance. In such cases, palliative chemotherapy is provided. Palliative chemotherapy requires both lower drug toxicity and reasonable efficacy; however, data regarding such palliative chemotherapy are limited. C-MOPP, which consists of a combination chemotherapeutic regimen consisting of cyclophosphamide, vincristine, prednisolone and procarbazine, can be administered in an outpatient setting without hospitalization. This regimen was originally reported 40 years ago and has been used in the treatment of Hodgkin lymphoma.[3-8] The efficacy of the C-MOPP regimen against follicular lymphoma has also been reported.[9,10]

In our institution, we have used C-MOPP as a palliative therapy, even aiming at tumor reduction prior to the follow-on cure-oriented hematopoietic stem cell transplantation (HSCT). In the present retrospective analysis, we have evaluated the efficacy and safety of C-MOPP with or without rituximab regarding previously treated aggressive non-Hodgkin lymphoma (NHL).

Patients and methods

Patients

The records of all of the patients previously treated for aggressive non-Hodgkin lymphoma with the C-MOPP chemotherapy regimen from 1999 to 2013 were obtained from the National Cancer Center Hospital database. In this study, we defined aggressive lymphoma as intermediate- or high-grade histopathologic subtypes (diffuse large B-cell lymphoma, mantle cell lymphoma, Burkitt lymphoma, peripheral T-cell lymphoma, extranodal NK/T-cell lymphoma, nasal type and others). In the 89 patients, we reviewed all of the assessable characteristics, pathology, treatment and follow-up information using patient charts. All of the pathologic data were confirmed at our institution (by H.T. and A.M.).

Treatment and evaluation

C-MOPP was administered as follows shown in the schematic in Figure 1. The cyclophosphamide dose was modified from the original;[11] it was 350 mg/m^2 on days 1 and 8. Vincristine (1.0 mg/m^2) was administered on days 1 and 8, prednisone (60 mg daily orally) on days 1ï 3 and 8ï 10, and procarbazine (100 mg) on days 1ï 14 repeated every 28 days. The dose of cyclophosphamide was 350 mg/m^2, which is the most frequently used dose in Japan.[12,13] The number of delivered cycles, modification of dose and duration of administered procarbazine were determined according to the physicianôs judgment. Since September 2003 when rituximab was approved in Japan, R-C-MOPP

therapy has been preferred in cases with CD20 positive B-cell lymphoma.

Manufacturer names for all of the products used in the present study are as follows. Cyclophosphamide, prednisolone: Shionogi Pharmaceutical Company, Ohsaka, Japan. Vincristine: Nipponkayaku Company, Tokyo, Japan. Procarbazine: Chugai Pharmaceutical Company, Tokyo, Japan. Rituximab: Zenyaku Kogyo, Tokyo, Japan.

Tumor response was evaluated by computed tomography (CT) scans after one or more cycles. Response was defined according to the RECIST criteria[14], because no patients underwent PET/CT. Bone marrow aspiration or biopsy to confirm CR were done only in cases with bone marrow infiltration positive before the treatment.

Toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Institutional review board approval was obtained for this study.

Statistical analysis

Progression-free survival (PFS) was calculated from the date of commencement of C-MOPP therapy to the date of documentation of clinical progression, the start of the next therapy, death from any cause or the last follow-up visit. Overall survival (OS) was calculated from the date of commencement of C-MOPP therapy to the date of death from any cause or the last follow-up. The probabilities of PFS and OS were evaluated using the Kaplan-Meier method.

Results

Baseline characteristics

Out of the 89 patients, 55 (62%) were diagnosed with diffuse large B-cell lymphoma (DLBCL), 17 (19%) with peripheral T-cell lymphoma or not otherwise specified lymphoma (PTCL, NOS) and 17 (19%) with miscellaneous lymphoma (Table 1). Among the 55 patients with DLBCL, the diagnoses of 11 cases were as follows: transformed follicular lymphoma (FL) in three; transformation from chronic lymphocytic leukemia/small lymphocytic lymphoma in one; DLBCL with FL in three; DLBCL with nodal marginal zone lymphoma in two; DLBCL with mucosa-associated lymphoma tissue (MALT lymphoma) in one; and gray zone with Hodgkin lymphoma in one.

The median number of regimens was 2 (range, 1-5). Eighty six patients (97%) had previously been treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOP-like chemotherapy, and the rest of other 3 patients had entered phase II clinical trial of more intensive therapy as a front line chemotherapy. Main salvage regimens before C-MOPP therapy were ESHAP (N=25), EPOCH (10) and ICE (5), and two patients were treated with darinaparsin or everolimus as Phase I studies. The median time from the last systemic chemotherapy was 3 months (range

0-105), and 63 patients were administered C-MOPP within 1 year from the last treatment. Eleven patients (12%) had undergone autologous or allogeneic stem cell transplantation prior to C-MOPP. Fifty-five patients (62%) were aged ¸ 65 years when they commenced treatment with the C-MOPP regimen, and they were not considered as candidates for subsequent stem cell transplantation (SCT).

Treatment combination and modification

Among the 55 patients with DLBCL, 17 (31%) received rituximab. The remaining 38 DLBCL patients were treated without rituximab, because they were treated before the drug was approved (n=25), after rituximab failure (n=6), or CD20 was negative (n=4) or unknown (n=3).

The median number of cycles of C-MOPP was four (range, 1ï 19) (Table 2). In 25 patients (28%), tumor shrinkage was observed and the therapy was discontinued (Table 3). Disease progression (n=49; 55%) resulted in discontinuation of C-MOPP therapy. Four patients stopped the therapy because of severe toxicity; two had pneumonitis, one had pneumonia and one had bone marrow suppression and liver damage. After discontinuation of C-MOPP, forty-four patients (49%) received different chemotherapy and twelve patients (14%) underwent allogeneic HSCT; twelve patients were able to undergo high-dose chemotherapy followed by allogeneic SCT, when progression was not shown in 9 cases, or when other subsequent salvage therapy was

effective in the rest of 3 cases. Four patients (5%) received palliative radiation therapy, and 28 (32%) had supportive care only.

The dose of procarbazine is shown in Table 4. In patients with severe myelosuppression or drug eruption, the procarbazine dose was reduced. One patient was given an escalated dose to increase efficacy, taking into consideration myelosuppression.

Outcome

The best tumor responses during the treatment period were assessable in 75 cases, among which, 28 patients obtained CR, 5 obtained PR, 17 obtained SD, and 25 obtained PD (Table 5). Overall response rate (ORR) was 37% (33/89), 43% in DLBCL, and 17% in PTCL-NOS. The response was translated into the survival; The median PFS of patients who achieved CR by C-MOPP was 33.1 months where as those with PR was 2.7 months (Table 6).

After a median follow-up of 61 months for the censored patients, 80 (90%) clinically progressed. The median time to progression was 7 (range, 1ï 149) months, and the estimated 1-year PFS rate was 33% (the number of events was 53). The median OS time was 17 (range, 1ï 152) months, and the estimated 1-year OS rate was 61% (the number of events was 33) (Figs.2A and B). In DLBCL and PTCL-NOS patients, the 1-year PFS rates were 37% and 17%, and the 1-year OS rates were 61% and 64%,

respectively (Figure 3).

The median PFS was also as long as 10.6 months among cases who had had achieved CR after previous CHOP or CHOP-like regimens. In the CHOP refractory cases, the median PFS was 2.7 months. Only 2 patients responded over 12 months, and their procarbazine relative dose intensity were >75% (Table 6).

Eighty-one patients were treated in an outpatient setting. The hematological toxicities of leukopenia and neutropenia were common (Table 7). Febrile neutropenia occurred in 11 patients (12%), grade 3 pneumonitis occurred in two and pneumonia in one. Secondary primary malignancy was observed in two patients; both had gastric cancer and both died from secondary malignancies without relapse of the lymphoma.

Discussion

In our study, 52 patients (58%) were aged >65 years, 15 patients (16%) received >2 previous systemic chemotherapies, 11 patients (12%) relapsed after high-dose chemotherapy (one patient underwent both auto and allo SCT), and 63 patients (71%) were in advanced stage when we started C-MOPP, and in that conditions, palliative chemotherapy or novel agent study is definitely required.

In the cases where CHOP therapy is the standard therapy and once CHOP therapy had some efficacy, we could use the same therapy, however, anthracyclin needed to be omitted due to the cumulative dose, and the 5th ónovelôagent,

procarbazine, was added instead, which constituted C-MOPP therapy, which used to be an old standard decades ago for treatment of aggressive lymphoma. Moreover, we supposed the known low toxicity level and the convenience that allows outpatient management was suitable for palliative settings.

The therapy was originally reported as a treatment for Hodgkin lymphoma. In addition, Longo et al. reported that this regimen was also effective in the treatment of FL.[9] These authors evaluated 79 newly diagnosed nodular mixed lymphoma patients including 33 who had received C-MOPP with or without radiotherapy. They found that 60 patients (76%) achieved complete remission, and 31 of these patients (52%) remained in remission throughout a median follow-up time of 7 years.[9] Recently, Fesler et al. reported the outcome of R-C-MOPP for untreated or relapsed follicular lymphoma. Among the relapsed patients (n=12), the overall response rate was 75%.[10]

We intended to use this regimen as a palliative chemotherapy. There have been a number of studies regarding cure-oriented therapeutic options for aggressive NHL, but few studies concerning palliative options. Palliative treatments need to be performed in an outpatient setting, with both lower intensity and toxicity, even if the effectiveness is limited to some extent. Nelson et al. reported the outcome of treatment using the CEPP(B) regimen that consists of cyclophosphamide, etoposide, procarbazine and prednisone with or without bleomycin, for patients with relapsed aggressive NHL.[15] The study population consisted of 44% of patients who were aged

1 ¸ 60 years, and a 72% overall response rate with a median survival time of 12 months
2 was reported.[15] Gemcitabine can achieve an overall response rate of 20ï 60% in
3 refractory NHL.[16-18] The GDP regimen (gemcitabine, dexamethasone and cisplatin) is
4 also available for the treatment of refractory B-NHL outpatients.[18] Among the 17
5 patients who did not undergo auto SCT, the median time to progression was 3.1 months.
6 Recently, treatment using bendamustine plus rituximab resulted in a 63% overall
7 response rate in patients with relapsed DLBCL, and the median time to progression was
8 6.7 months.[19]
9 Compared with the findings of these studies, the PFS rate at 1 year after
10 treatment using C-MOPP was as high as 33% in the present study, and the median
11 duration to progression was 7 months. Forty patients (45%) responded to C-MOPP,
12 which represents superior efficacy to that achieved in the above studies. Because we did
13 not prospectively evaluate tumor size using CT scans, the date of progression might
14 have been missed or detection delayed. Even accepting such a potential bias, the OS at 1
15 year was 63%, which is again favorable data.
16 In the present study, grade 3ï 4 hematologic toxicities occurred in 20ï 55% of
17 patients; these patients required the administration of granulocyte-colony stimulating
18 factor for prophylactic usage, blood transfusion and a reduction in the dose of
19 procarbazine. However, these therapies were well tolerated as a whole. Not all the
20 non-hematological adverse events were assessed, but 24 patients received more than 6

cycles of C-MOPP, among them five patients received more than 10 cycles without severe toxicities, and even subsequent allogeneic transplantation was successfully performed. Toxicities were lower and milder than those of gemcitabine, GDP and bendamustine plus rituximab regimens, which were associated with an incidence of 6ï 73% hematological adverse events.[18-19]

We showed responses in these palliative settings especially in relapsed cases after CHOP or CHOP-like regimens, which is translated to longer PFS and OS. These data could serve as a rationale for the use of C-MOPP as a current control treatment arm when the efficacy of a novel agent is evaluated.

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Figure legends

Figure1. Schema of C-MOPP

Figure 2. Survival of the patients. A. Progression-free survival. The survival time (months) was calculated from the date of commencement of C-MOPP to the date the physician recognized that the tumor had progressed. Bars indicate censored cases.

B. Overall survival. Bars indicate censored cases.

Figure 3. Survival of DLBCL and PTCL-NOS. A. Progression-free survival of DLBCL (solid line) and PTCL-NOS (dotted line). Bars indicate censored cases.

B. Overall survival of DLBCL (solid line) and PTCL-NOS (dotted line). Bars indicate censored cases.

Table 1. Baseline characteristics at the commencement of C-MOPP

Characteristics		Number (%) (n=89)
Histological subtype		
DLBCL		55 (62)
PTCL-NOS		17 (19)
AITL		9 (10)
ALCL		3 (3)
ATL		4 (4)
Blastic NK Lymphoma		1 (1)
Number of prior systemic chemotherapy regimens	1	37 (42)
	2	37 (42)
	3	8 (9)
	Ó4	7 (7)
Previously treated with anthracycline-containing therapy		89 (100)
Previously treated with rituximab-containing therapy		26 (29)
Prior SCT	Auto	9 (10)
	Allo	2 (29
Gender	Male	47 (53)
Age	Median (Range)	67 (22-81)
	>65	52 (58)
Ann Arbor stage	III, IV	63 (71)
LDH elevation	> Normal limit	62 (70)
Extranodal sites	Ó2	17 (19)
Performance status	Ó2	7 (8)
	unknown	3 (3)

Table 2. Number of cycles of C-MOPP delivered

Cycles	Number (%)
1	10 (11)
2	13 (15)
3	13 (15)
4	10 (11)
5	6 (6)
6	13 (15)
7	6 (6)
8	9 (11)
9	3 (4)
>9	6 (6)

Table 3. Reasons for discontinuation of C-MOPP

	Number (%)
Disease progression	49 (55)
Tumor shrinkage	25 (28)
Allo-SCT	9 (10)
Adverse event	4 (5)
Patientôs refusal	2 (2)

Table 4. Relative dose intensity of procarbazine

Relative dose intensity (%)	Number (%)
0-25	16 (18)
25-50	29 (33)
50-75	15 (17)
75-100	27 (30)
>100	2 (2)

Relative dose intensity was calculated as the delivered dose intensity divided by the planned dose intensity (Fig. 1).

Table 5. The best tumor response of C-MOPP

	Total (N=89)	DLBCL (N=55)	PTCL-NOS (N=17)
	N (%)	N (%)	N (%)
CR	28 (31)	20 (36)	3 (17)
PR	5 (6)	4 (7)	0 (0)
SD	17 (19)	7 (13)	6 (35)
PD	25 (28)	16 (29)	4 (23)
NE	14 (16)	8 (15)	4 (23)

Table 6. Survival according to response of C-MOPP by that of previous treatment

	Total	PFS, months	OS, months
	N	Median (range)	Median (range)
The best response of C-MOPP			
CR	28	33.1 (2.3-149.4)	NR (7.8-152.9)
PR	5	9.5 (0.8-12.7)	12.1 (3.9-25.1)
SD	17	5.0 (0.8-21.8)	22.7 (1.1-72.0)
PD	25	2.7 (0.3-16.9)	6.4 (1.0-18.8)
Survival according to the response to previous CHOP or CHOP-like treatment			
CR*	50	10.6 (0.1-149.4)	22.7 (1.4-152.9)
Non CR*	27	2.7 (0.1-45.2)	11.5 (1.0-103.3)

* Cases with CR or non-CR by previous CHOP or CHOP-like treatment.

Table 7. Incidence of adverse events

	Grade 3	Grade 4	Grade 3-4
	N (%)	N (%)	N (%)
Leukopenia	34 (38)	15 (17)	49 (55)
Neutropenia	28 (32)	18 (20)	46 (52)
Anemia	31 (35)	0 (0)	31 (35)
Thrombocytopenia	7 (8)	11 (12)	18 (20)
Febrile neutropenia	11 (12)	0 (0)	11 (12)

Figure1

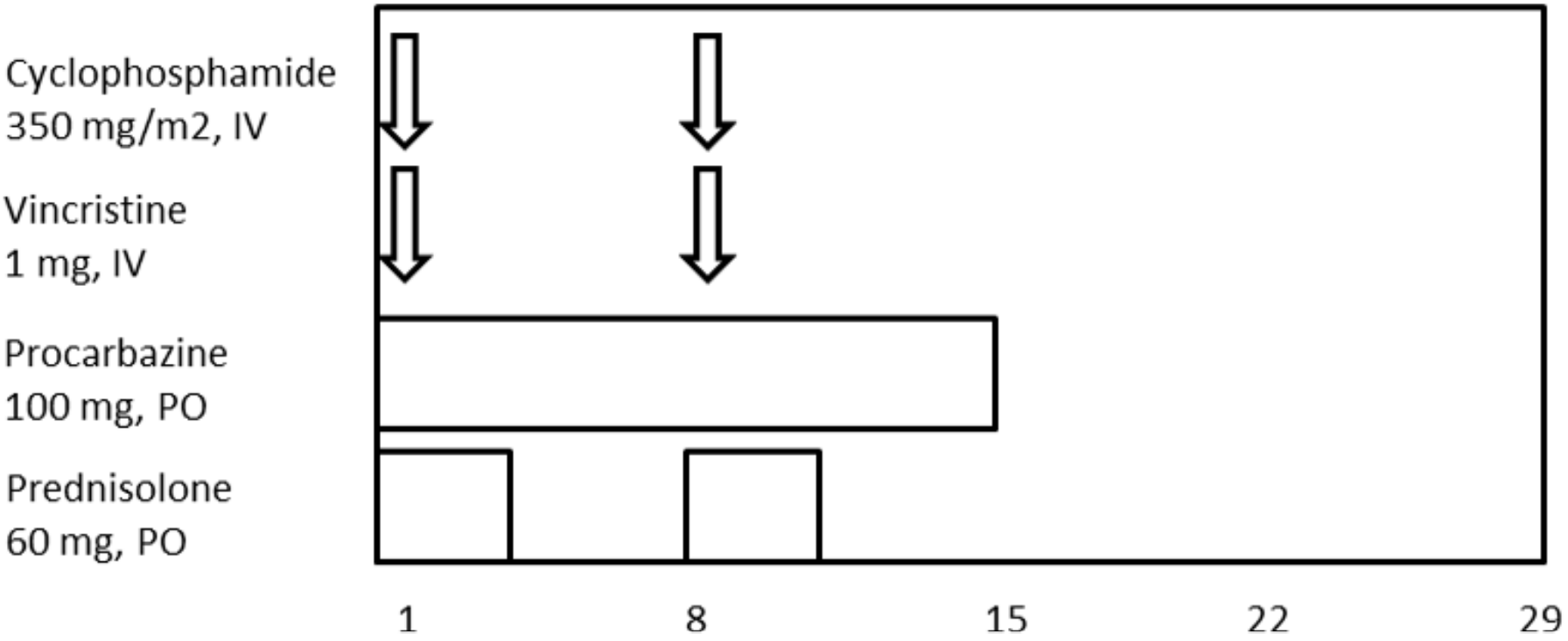
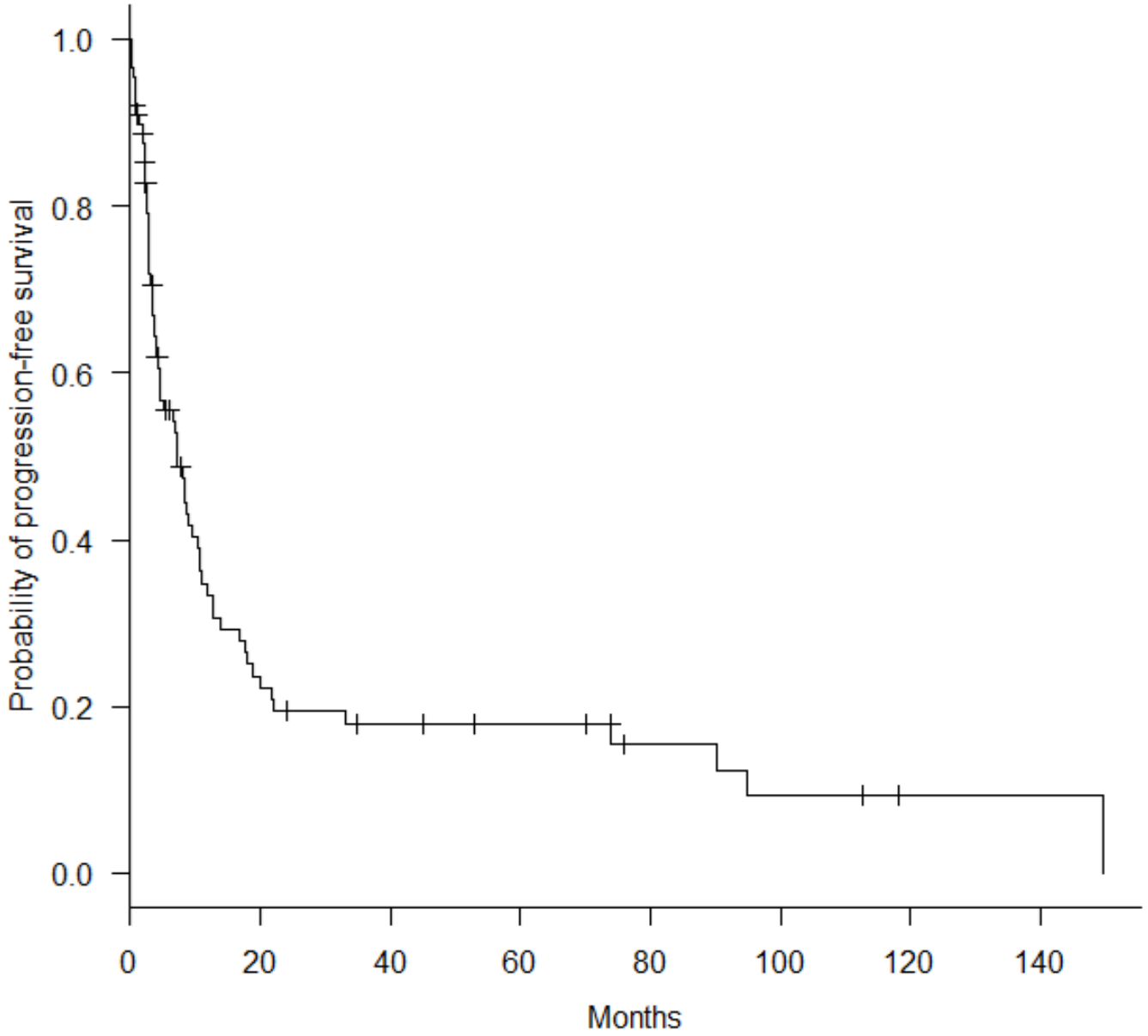

Cyclophosphamide
350 mg/m2, IV
Vincristine
1 mg, IV
Procarbazine
100 mg, PO
Prednisolone
60 mg, PO
1
8
15
22
29

Figure2.A.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Probability of progression-free survival
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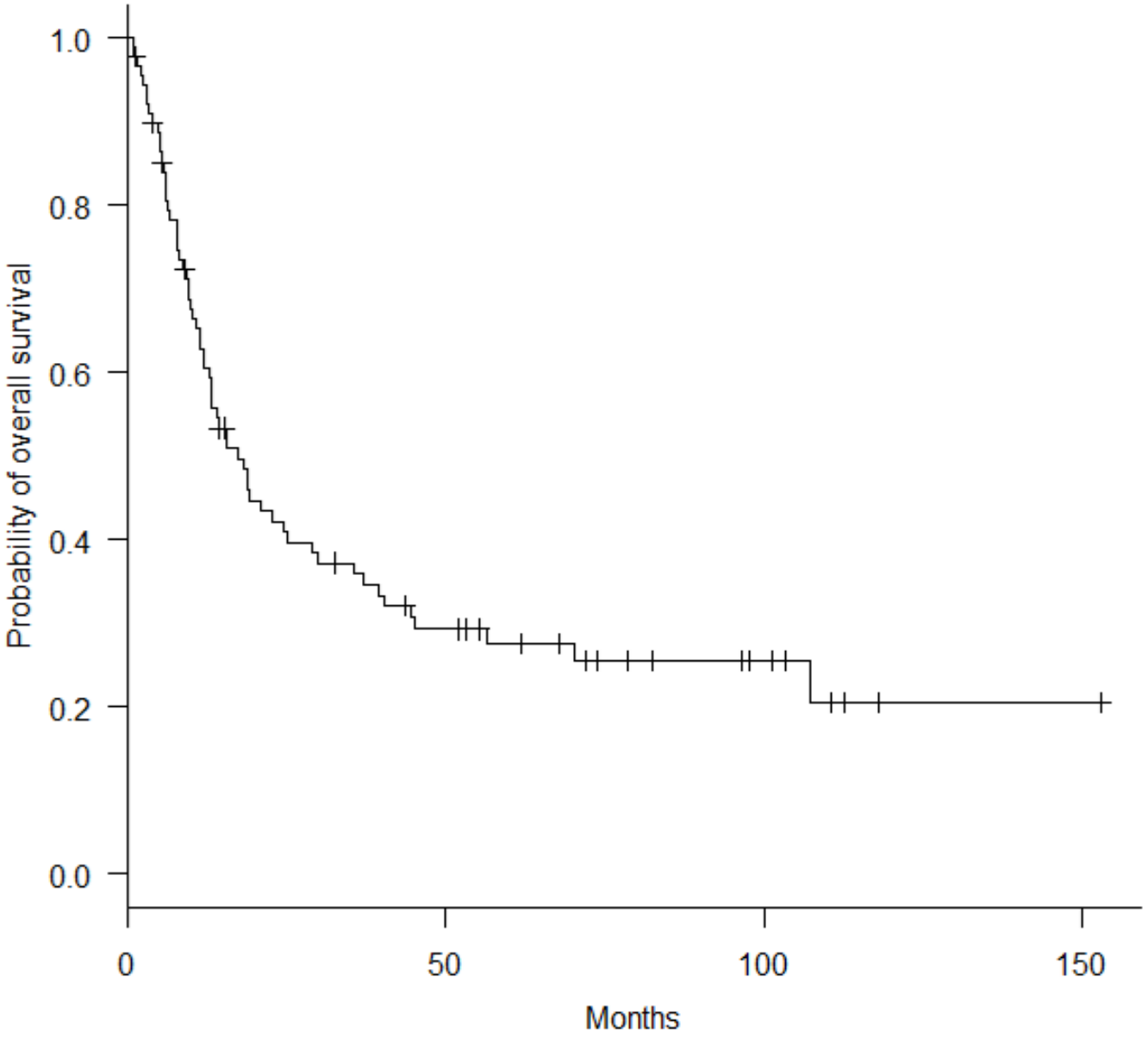
120
140
Months

Figure2.B.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Probability of overall survival
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50
100
150
Months

Figure3.A.

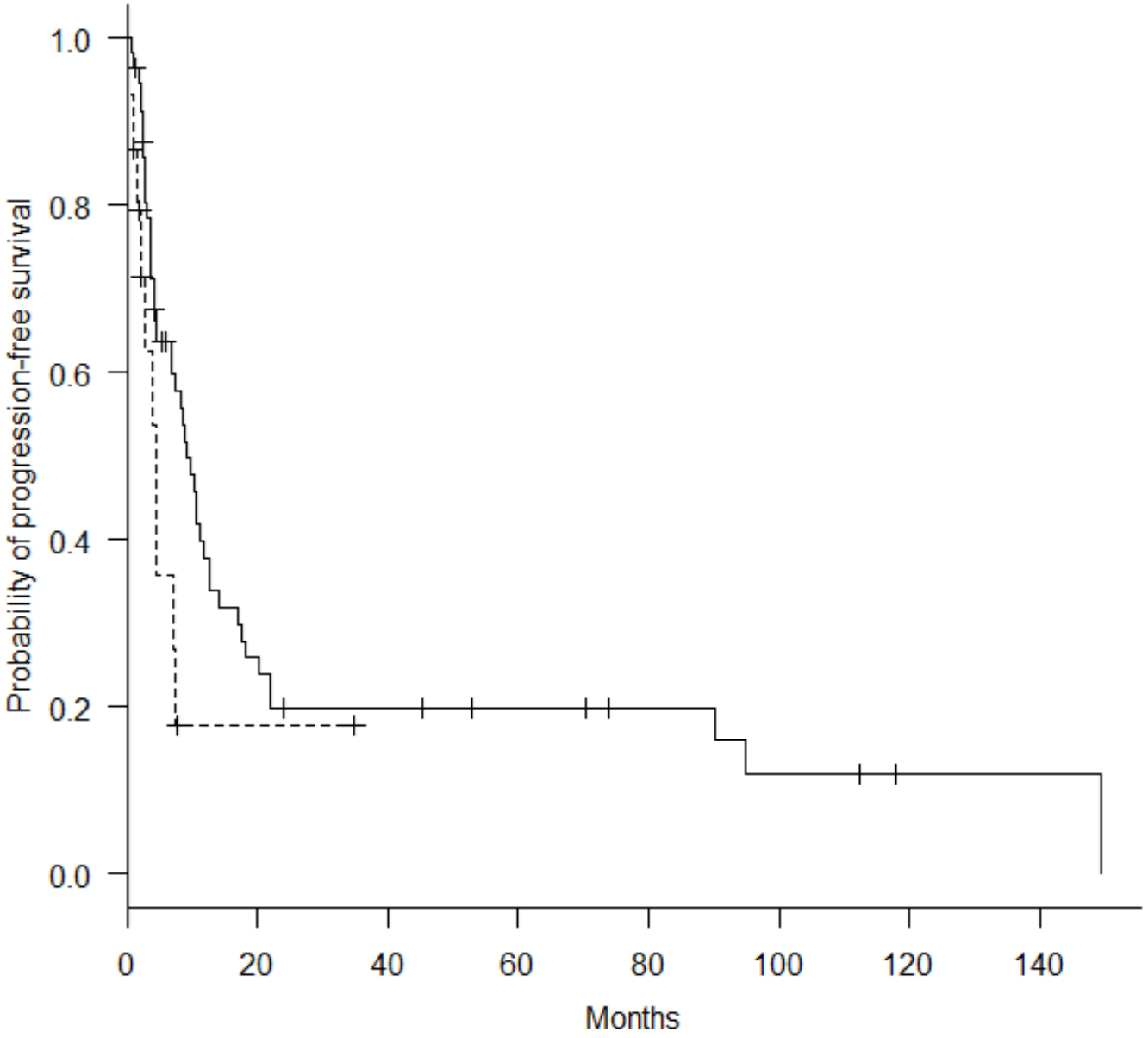
Probability of progression-free survival
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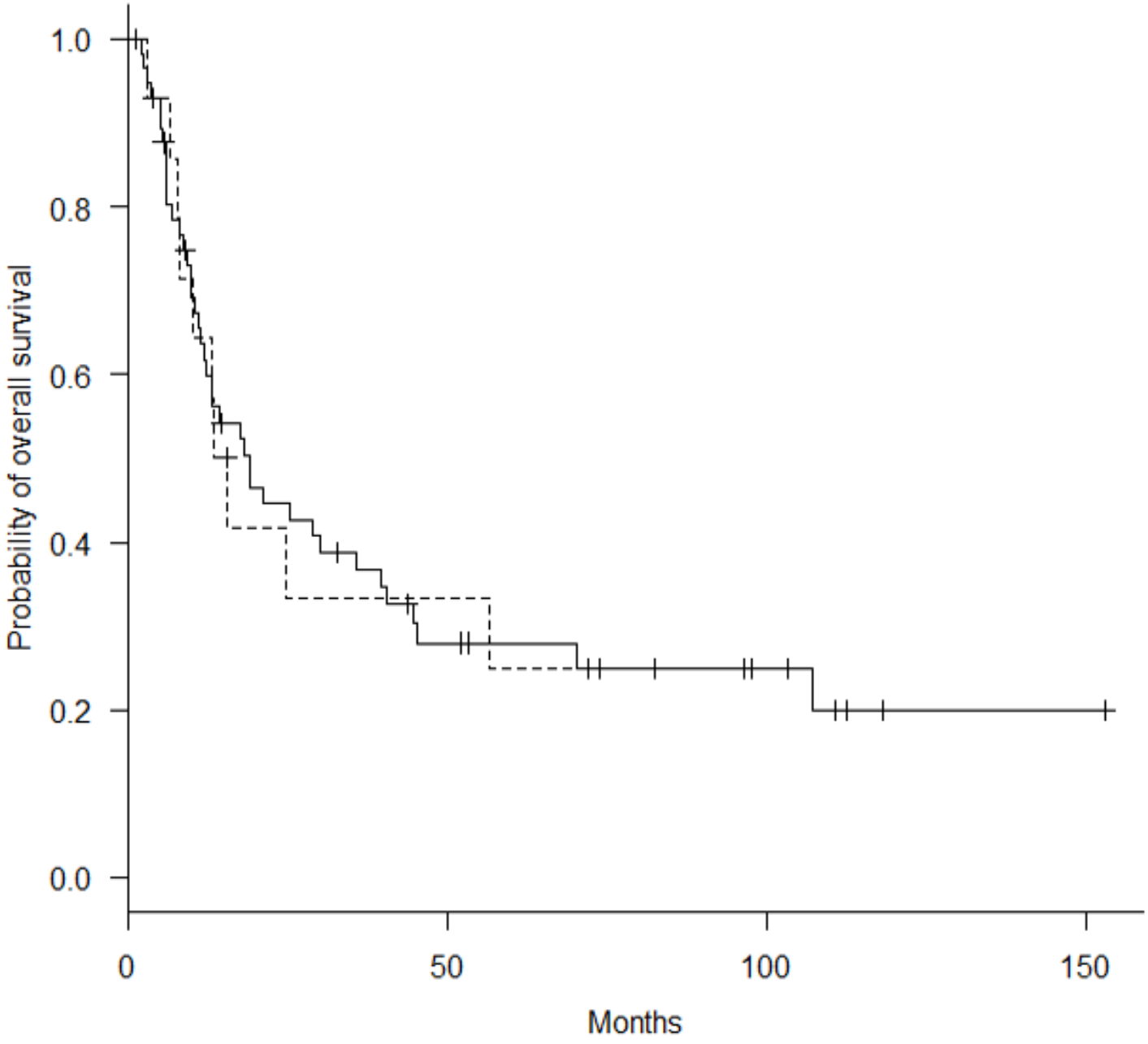
Figure3.B.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Probability of overall survival
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