Phase-II study of the new aza-anthracenedione, BBR 2778, in patients with relapsed aggressive non-Hodgkin's lymphomas

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Background and Objectives. BBR 2778 is a new aza-anthracenedione. Its activity against hematologic neoplasias in a mouse model is greater than that of doxorubicin or mitoxantrone. A phase-I study in patients with non-Hodgkin's lymphoma (NHL) showed that the drug has promising anti-tumor activity. Therefore, a phase-II study in patients with relapsed aggressive NHL was initiated.

Design and Methods. The primary objective was to determine the efficacy of 85 mg/m^2 BBR 2278 for a *q1w* $\times$3 treatment schedule (repeat day 29). Secondary objectives included the evaluation of response duration and safety in this open-label, non-randomized, multicenter trial. Patients with relapsed aggressive NHL according to the REAL-classification were included.

Results. Eight centers enrolled a total of 33 patients. The median age of these patients was 66 years (range 24-81). The majority of patients had diffuse large B-cell lymphoma (n=24) or mantle-cell lymphoma (n=7), pretreated with a median of 2 regimens. Confirmed responses included 5 complete and 4 partial remissions, with the period between the first appearance of response and any signs or symptoms of progression being up to 17+ months. The main toxicity was neutropenia.

Interpretations and Conclusions. These results indicate that 85mg/m^2 BBR 2778 in a *q1w* $\times$ 3 schedule is active in elderly and pretreated patients with relapsed aggressive NHL and was generally well tolerated. Thus, we recommend further clinical evaluation of this new compound in phase-III studies for the treatment of NHL.

Key words: BBR 2278, anthracycline, phase-II study, aggressive non-Hodgkin's lymphoma, anthracenedione.

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Anthracyclines form one of the most effective groups of cytotoxic drugs and are widely used in the treatment of solid tumors and hematologic malignancies.[1] However, the clinical use of these drugs is hampered by their acute and delayed cardiotoxicity.[2,3] The anthracycline-derived anthracenedione mitoxantrone is also known to induce cardiomyopathy. This toxicity is probably caused by its 5,8-dihydroxy substitution group.[4,5] Therefore, anthracenediones devoid of these hydroxyl groups were developed for possible clinical use. Nitrogen atoms were introduced into the anthraquinone chromophore in order to create additional hydrogen bonding and basic sites while maintaining the planar structure of the parent compound.

These modifications modulate the affinity of the resulting molecules for DNA and affect their interaction with topoisomerase II. Screening of different aza-anthracenediones led to the identification of BBR 2778 (6,9-bis {[(2-amino)ethyl]amino} - benzo[γ]isoquinoline - 5,10 - dione dimaleate, Figure 1). The mechanism of action of BBR 2778 is similar to that of mitoxantrone, including intercalation with DNA, strand breaks, and interaction with topoisomerase II.[6,7] *In vitro* studies showed a wide range of cytotoxic potency which was most pronounced in leukemias and non-small cell lung cancer.

Importantly, BBR 2778 had greater cytotoxic activity in P388- and L1210 murine leukemias than did mitoxantrone and doxorubicin and revealed a broader therapeutic range. Mice treated with BBR 2778 at doses that were equally effective as those of mitoxantrone showed no signs of acute or delayed cardiotoxicity.[8,9] On the basis of these data, a clinical phase I study in patients with relapsed and refractory malignant lymphoma was initiated. In this phase I study, BBR 2778 was well tolerated and showed antitumor activity in these heavily pretreated patients.[10] The recommended dose from this phase I study was 84 mg/m^2/d in a *q1w* $\times$ 3 treatment schedule (days 1, 8 and 15, repeat on day 29).

Two other phase I studies performed in patients with solid tumors found recommended doses of 112.5 mg/m^2 for a *q1w* $\times$ 3 schedule, every 4 weeks, like the schedule we used in lymphoma patients, and 180 mg/m^2 when the drug was given every three weeks.[11,12] Here, we report the results of a multicenter phase II study with BBR 2778 given as single agent to patients with relapsed, aggressive NHL.

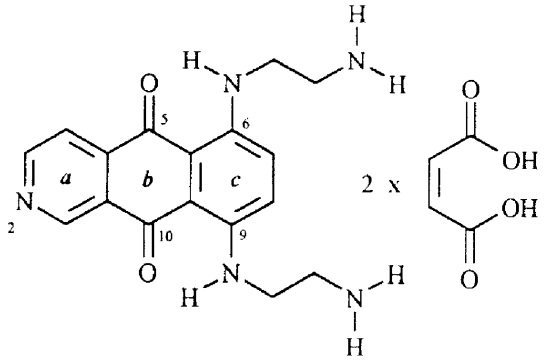

Figure 1. Structural formula of BBR 2778.

Design and Methods

Eligibility criteria

Eligible patients had bidimensionally measurable and histologically proven relapsed, aggressive NHL according to the REAL classification.[13] Patients could have received a maximum of three prior chemotherapy regimens containing anthracyclines. After anthracycline pre-treatment, a progression-free interval of 6 months before study entry was mandatory. If the previous regimen did not contain anthracyclines, earlier relapses could also be included. Other inclusion criteria were adequate bone marrow capacity (defined as neutrophils ≥ than 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin level ≥ 8 g/dL), WHO performance status of 2 or less, age 18 years or older, serum bilirubin levels ≤1.25 times and serum creatinine ≤1.5 times above the upper normal limit, cardiac function as measured by multiple gated acquisition-scan (MUGA-scan) with a baseline left ventricular ejection fraction (LVEF) ≥30%, no history of myocardial infarction within the last 12 months, no current history of angina, or any non-compensated active heart disease. The protocol was approved by the institutional ethics committees and patients had to give written informed consent to participation after the investigational nature of the treatment had been explained to them.

Treatment and study design

This clinical trial was an open-label, non-randomized, non-comparative phase II study. The primary objective was to evaluate the efficacy of BBR 2778 as determined by the response rate. Secondary objectives included the response duration, the progression-free survival, and the safety with particular regard to the cardiac toxicity profile. BBR 2778 was diluted in 500 mL isotonic saline and administered at a dose of 85 mg/m^2/d intravenously in a *q1w* × 3 schedule, every 4 weeks. Antiemetic prophylaxis (5HT-3 antagonists) was administered before each infusion of BBR 2778. Treatment within a cycle was continued on day 8 and 15 if neutrophils were ≥1.0×10^9/L, and platelets ≥75×10^9/L. Otherwise, the administration was delayed until recovery of these hematologic parameters. Before each subsequent cycle neutrophils had to be ≥1.5×10^9/L, and platelets ≥100×10^9/L. Non-hematologic toxicities had to be resolved to less than grade 2 (NCI CTC). If these criteria were not met on day 29, treatment was postponed for 1 to 2 weeks until recovery. If after two weeks these values were not reached, the dose was reduced by 20%. If, despite this modification, these values were not reached at week 6, the protocol called for the patient to be taken out of the study. Granulocyte colony-stimulating factor support was allowed in accordance with the updated guidelines of the American Society of Clinical Oncology.[14] A 20% dose reduction was also foreseen for all grade 3 or 4 non-hematologic toxicities as well as for grade 4 thrombocytopenia. Patients received up to six courses of treatment unless there was progressive disease. After the study, treatment was discontinued and responding patients were followed at 3-month intervals.

Toxicity and response evaluation

Safety assessments were performed before each cycle for all patients who had received at least one cycle of study treatment. Blood chemistry analyses, including renal and liver function tests, were performed every 4 weeks and blood counts were performed weekly. Cardiac function was monitored closely by MUGA-scan and electrocardiographs every second cycle. Toxicity was evaluated according to the NCI-CTC grading system.[15] Response was evaluated in accordance with WHO criteria and thus had to be confirmed by two measurements separated by at least 4 weeks. Any response determined by a single measurement was indicated as unconfirmed and not included in the overall response rate analysis. Briefly, complete response (CR) was defined as the complete disappearance of all detectable clinical or radiographic evidence of disease, partial response (PR) as a decrease of more or equal to 50% of the sum of the products of the greatest diameters (SPD), and stable disease (SD) as less than a 50% reduction in these parameters without evidence of progression of the disease. Progressive disease (PD) was defined as the appearance of any new lesion or an increase of 25% or more in the size of any measurable or evaluable lesions, or the progression of non-measurable disease.[16]

Statistical analysis

Statistical evaluation was performed using descriptive statistics and patient's data listings. No hypothesis testing was planned. Response rates were calculated on the basis of an intent-to-treat analysis. The statistical software SAS 6.12 was used to compute the study data.

Results

Patients' characteristics

Eight centers in France (n=3) and Germany (n=5) participated in the trial and enrolled a total of 33 patients between 02/00 and 03/01. Their median age was 66 years (range 24-81 years) with the majority of patients (27/33) being older than 60 (Table 1). Eighteen patients were male. WHO performance status was 1 in 26/33 patients. The histologic diagnosis in most cases was diffuse large B-cell lymphoma (n = 24) and mantle cell lymphoma (n = 7). Two other patients suffered from a transformed follicular high grade lymphoma and a relapse of a previously diagnosed high grade variant of a monocytoid B NHL. The majority of patients (n = 25; 76%) had advanced stage disease (stage III/IV), and 15 (45%) had extranodal disease. A median of 2 prior chemotherapy regimens (range 0-5) had been administered. Two patients had received prior high dose chemotherapy with autologous peripheral blood stem cell transplantation and five patients had had prior radiotherapy. The median interval from the last prior chemotherapy was 123 days (6 days to 5 years). Prior exposure to an equivalent dose of doxorubicin was 300 mg/m^2 (range 110 to 600 mg/m^2). Overall, a total of 103 cycles of BBR 2778 were administered with a median of 2 cycles per patient (range 1-6). Twenty-seven patients received the full doses of planned therapy on days 1, 8 and 15. In the remaining patients, the infusions on day 8 and/or day 15 were omitted due to hematotoxicity or PD. Only 6 patients (18%) completed the planned 6 cycles during the study period; 27 (82%) discontinued therapy prematurely, most of them (n=19; 58%) because of PD. Other reasons included non-hematologic toxicities (n=4; 12%), patient's refusal (n=3; 9%), and fatal septicemia in one patient (3%).

Toxicity

Hematologic toxicity

Neutropenia was the most relevant hematologic toxicity (Table 2). In 19/33 patients (58%, 48/103 cycles) grade 3 or 4 neutropenia occurred; this was generally brief, lasting a median of 7.5 days (range 2-54 days). The median duration of neutropenia did not increase with the number of cycles given

Table 1. Patients' characteristics (total n = 33).

Characteristic	Patients No.	Patients %
Sex (male/female)	18/15	55/45
Age [years]		
Median	66	
Range	24-81	
> 65	22	67
Performance status		
0	4	12
1	26	79
2	3	9
Histology [REAL]		
Diffuse large B-cell	24	73
Mantle-cell NHL	7	21
Other	2	6
Time from last prior chemotherapy		
Median	123 days	
Range	6 days - 5 years	
No. of prior therapeutic regimens		
0	1	3
1	6	18
2	11	33
3	11	33
≥ 4	4	12
Stage at study entry		
I/II	8	24
III	6	18
IV	19	58
IPI risk group (age-adjusted)		
Missing	4	12
Low (0, 1)	2	6
Low-intermediate (2)	15	46
High-intermediate (3)	11	33
High (4)	1	3

Table 2. Hematologic toxicity by adverse event: worst grade (total n. of patients = 33).

	CTC- Grade 2	CTC- Grade 3	CTC- Grade 4
N. of patients with neutropenia	3	6	13
N. of patients with lymphopenia	–	8	19
N. of patients with anemia	12	1	1
N. of patients with thrombocytopenia	3	2	–

Table 3. Grade 3 and 4 neutropenia during the treatment period.

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Median time to nadir [days]	23.5	15	15	15	21	14
Median time to recovery to grade ≤ 2 (range) [days]	7.0 (2, 22)	13.0 (3, 54)	7.0 (5, 18)	12.0 (6, 35)	8.0 (6, 12)	7.0 (6, 11)
Median nadir (range) [10×9/L]	0.441 (0.00,0.94)	0.660 (0.10,0.86)	0.720 (0.25,0.91)	0.732 (0.07,0.92)	0.700 (0.40,0.97)	0.616 (0.47,0.68)

Table 4. Patients with absolute LVEF decrease > 10%, possibly related to BBR 2778 treatment (LVEF below 50%).

Prior cardiac condition	*Age*	*Prior dx. equivalent dose (mg/m²)*	*No. of cycles applied*	*BBR 2778 cumulative dose (mg/m²)*	*Follow-up (mo.)*	*LVEF [%] (MUGA-scan) Baseline*	*Last cycle*	*Last FU*
Normal	79	270	6	1.505	19	60	32	26
Coronary heart disease Low output syndrome	65	300	5	1046	17	39	25	nd*
Normal	66	425	5	1273	7	43	39	30°

**nd: not done, clinically persisting symptoms of low cardiac output; °MUGA-scan at 4 months. Follow-up at 7 months without clinical symptoms of congestive heart failure. dx.: doxorubicin.*

nor did the median nadir decrease (Table 3). Nevertheless, delay of treatment due to neutropenia occurred in 16 patients (38/103 cycles) necessitating dose reduction in 5 patients. One patient developed neutropenic septicemia with a fatal outcome. This patient died 13 days after the last infusion of the 4th course in septic shock, possibly due to drug-related leukopenia. Grade 3 and 4 lymphopenia occurred in 27 patients (82%), whereas grade 3 or 4 anemia or thrombocytopenia was observed in only 2 patients (Table 2).

Non-hematologic toxicity

A significant absolute decrease of more than 10% of the left ventricular ejection fraction (LVEF), as measured by MUGA-scan, was detected in 3 patients. This was possibly related to the treatment with BBR 2778. All three patients had been pretreated with anthracyclines (Table 4). Two had a low cardiac output at baseline (39% and 43%). In one of these patients, the decrease to a LVEF of 29% occurred after cycle 4 and caused clinical symptoms (dyspnea). Continuation of BBR 2778 treatment after appropriate treatment and subsequent resolution of the cardiac symptoms was associated with a further LVEF decrease to 25% and study termination. In the other two patients, low cardiac output developed 4 weeks and 4 months after study termination. In one of these two patients, LVEF decreased from 60% at baseline to <30% during the follow-up period and was accompanied by cardiac symptoms, whereas the other patient showed no clinical symptoms. Other ≥ grade 3 non-hematologic toxicities for which a relationship with BBR 2778 could not be excluded were observed in very few patients and consisted of hepatobiliary disorder with an increase of alkaline phosphatase (n = 1), arthritis (n = 1), and asthenia (n = 1). All events resolved completely. Other drug-related events observed were alopecia in 3 patients, and mild or moderate nausea occurring in 10 patients.

Table 5. Response to BBR 2778.

	n	*(%)*
Complete response	5	15
Partial response	4	12
Confirmed response rate	9	27
95% confidence interval		13-46
Partial response, unconfirmed	5	15
Stable disease	3	9
Progressive disease	13	39
Not evaluable	3	9

Tumor response

Response to BBR 2778 and the patients' detailed characteristics are listed in Tables 5 and 6. CR was confirmed in 5 patients, PR in 4 patients. The period elapsing from the first appearance of response to any signs or symptoms of progression was up to 17+ months for patients who had a CR while on treatment. On the basis of an intent-to-treat analysis, the overall response rate was 27% with a median progression-free survival of 106 days (follow-up is still ongoing). Of the seven patients with

Table 6. Characteristics of responding patients.

Sex	Age	Histology	Stage	IPI score	No. of prior Ctx	Prior dx. equivalent - dose (mg/m^2)	Interval to last prior Ctx (days)	Response	Response duration §(months)
F	79	Diffuse large B-cell lymphoma	II	2	3	264	57	CR	17+
F	65	Diffuse large B-cell lymphoma	IV	NA	2	400	38	CR	8.6
M	72	Diffuse large B-cell lymphoma	II	NA	2	400	199	PR	5. 0
M	66	Transformed follicular lymphoma	IV	3	3	410	55	PR	24+*
F	65	Mantle cell lymphoma	IV	2	2	300	36	CR	15.2
F	72	Diffuse large B-cell lymphoma	IV	3	3	300	39	PR	2,3
F	41	High grade variant monocytoid B -NHL	IV	1	2	300	265	CR	10,5 +
F	60	Diffuse large B-cell lymphoma	III	2	4	400	36	PR	3,7
F	55	Diffuse large B-cell lymphoma	III	1	1	300	363	CR	11+

*NA: not available; *PR after BBR 2778 therapy was consolidated with radiotherapy; §period elapsing from the first appearance of response to any signs or symptoms of progression. dx: doxorubicin.*

relapsed mantle cell lymphoma, only one patient responded (CR, 15 months). In 5 patients, a transient but significant (> 50% tumor reduction) response to BBR 2778 was observed by a single measurement, which was, however, unconfirmed upon re-evaluation. Thirteen patients had progressive disease, resulting in premature study termination. With a follow-up period of 12 months after study termination 19 patients have died from disease progression.

Discussion

The following major findings emerge from this phase II study: (i) with an overall response rate of 27%, the new aza-anthracenedione, BBR 2778, is active in relapsed aggressive NHL at doses of 85 $mg/m^2/d$ given as monotherapy in a $q1w \times 3$ schedule; (ii) leukopenia is the major hematologic toxicity; (iii) in general, BBR 2278 is well tolerated but cardiac toxicity cannot be excluded in anthracycline-pretreated elderly patients.

This phase II study on the effect of BBR 2778 included predominantly elderly patients with multiply relapsed, aggressive NHL. The majority of patients presented with a second or subsequent relapse after a short median time to relapse (123 days). In this cohort of patients with an unfavorable prognosis, an overall confirmed remission rate of 27% was achieved and included some patients with a long lasting and ongoing response. In addition, 5 patients showed a partial, albeit only transient remission, indicating the activity of the drug. It is difficult to compare these response rates to results reported from other trials for several reasons: (i) there are only few reports on the activity of single agents in this setting; (ii) confirmatory studies are either lacking even for frequently used combination regimens or fail to confirm the previous studies;[17,18] (iii) most studies include only a very limited number of patients with marked heterogeneity in terms of histology and prior treatment; (iv) information on the activity of anthracycline derivatives after anthracycline failure is very limited. Given these limitations, the observed efficacy of BBR 2778 seems to be superior to that reported for drugs such as etoposide, gemcitabine, paclitaxel, cisplatinum, or mitoxantrone when used as single agents.[19-24] Liposomal daunorubicin, as a single agent, has been tested in relapsed NHL, but 70% of patients suffered from indolent lymphoma.[25] Thus, the results are not comparable to the data presented here. Although the activity of BBR 2778 is encouraging, combination regimens including DHAP (dexamethasone, cytarabine, cisplatinum), DIZE (dexamethasone, idarubicin, ifosfamide, etoposide), EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone), or

CCOP (cyclophosphamide, pegylated liposomal daunorubicin, vincristine, prednisone) showed higher response rates, but it should be noted that the toxicity of most of these regimens was higher.[26-29] A subgroup analysis for patients suffering from mantle cell lymphoma in this study would not be meaningful because of the small number of patients. Nevertheless, it can be noted that only one of seven patients with mantle cell lymphoma responded to BBR2778, confirming the poor prognosis of patients with relapsed mantle cell lymphoma.[30]

On the basis of the results of this phase II study, BBR 2778 warrants further clinical evaluation in diffuse large B-cell lymphoma.

Pre-clinical experiments and the phase I studies of BBR 2778 indicated that leukopenia was the main toxicity of this drug.[10] This was confirmed in the present phase II study with grade 3/4 lymphopenia occurring in 82% of patients and neutropenia in 58%. Whereas the lymphopenia remained clinically irrelevant, the neutropenia frequently led to delay of treatment (37% of cycles) and dose reduction (15% of patients). Leukopenia was most pronounced on day 15 of a given cycle, indicating that the $q1w \times 3$ schedule is not ideally suited for longer treatment with this aza-anthracenedione. However, no patient had to be withdrawn from the study because of prolonged neutropenia and no cumulative myelotoxicity was observed during the study period. Febrile episodes occurred in four patients, but these were promptly resolved after antibiotic therapy in three. One patient, who had a markedly reduced bone marrow capacity because of multiple prior chemotherapies, died in neutropenic sepsis. This patient was refractory to therapy with chlorambucil and was included in this study with progressive disease. After two cycles of BBR 2778 a PR was attained and, therefore, treatment continued although delays between drug administrations occurred because of the prolonged leukopenia. After the fourth cycle the patient developed a septic syndrome. The fatal course of this complication might have been, in part, due to the extensive prior chemotherapy regimens. Apart from this case, neutropenia was generally uncomplicated; anemia and thrombocytopenia were not accompanied by clinically apparent problems.

Preclinical evaluation of BBR 2778 in animal models had shown that equally effective doses of this drug, in comparison with daunorubicin and mitoxantrone, did not cause delayed cardiotoxicity.[8] Since this might be an advantage over these latter two compounds, cardiac function was monitored closely in this phase II study. A decrease of LVEF was detected in three elderly patients (9%) who had been pretreated with anthracyclines. Two of these patients had a LVEF <50% at study entry. This was in accordance with the inclusion criteria of the present trial (LVEF > 30%) permitting the inclusion of patients with impaired cardiac function. The LVEF decrease observed was, perhaps, caused by BBR 2778 suggesting a cumulative toxicity in these patients as described for anthracyclines and anthracenediones.[3,31,32] However, the cardiotoxicity of BBR 2778 might be overestimated from the present trial because of the high-risk profile of the study population. On the other hand, given the high proportion of patients with progressive disease receiving not more than two courses of BBR 2778, the median cumulative dose BBR 2778 administered was moderate (1020 mg total). This, conversely, could result in an underestimation of its toxicity. To clarify unambiguously the important question of a possibly more favorable cardiac risk profile associated with BBR 2778, a randomized trial comparing BBR 2778 with either an anthracycline or mitoxantrone is warranted. We, therefore, recommend establishing the maximum tolerated dose of BBR 2778 in the CHOP-like regimen BBR 2778-COP (cyclophosphamide, BBR 2778 instead of doxorubicin, vincristine, prednisone). This schedule could then be compared to CHOP in the first-line therapy of diffuse large B-cell lymphoma in a phase III study. In this setting, the antitumor activity as well as the cardiotoxic potential of BBR 2778 could be clearly assessed.

In summary, BBR 2778 administered as a single agent is active in patients with relapsed, aggressive NHL and was generally well tolerated. Further clinical evaluation of this new compound in phase III studies is underway.

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Contributions

Besides GC (from Novuspharma S.p.A.), all the authors in this multicenter trial were involved in the design of the study, revised the manuscript critically and approved the final version. In addition, AE and GC were responsible for analysis of the data. PB wrote the first draft of the manuscript.

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Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received February 17, 2003; accepted June 13, 2003.

In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

What is already known on this topic

BBR 2778 is a novel cytotoxic drug whose structure is similar to that of mitoxantrone. With respect to this latter, BBR 2778 appears to have greater cytotoxic activity and lower cardiotoxicity.

What this study adds

This phase-II study shows that BBR 2778 administered, as a single agent, is active in patients with relapsed, aggressive non-Hodgkin's lymphoma and is generally well tolerated.