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Outcome After First Relapse in Children With Acute Lymphoblastic Leukemia: A Population-Based Study of 315 Patients From the Nordic Society of Pediatric Hematology and Oncology (NOPHO)

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This study reports the outcome after relapse of acute lymphoblastic leukemia (ALL) in a population-based study of 809 children over 1 year of age diagnosed July 1981 through June 1986 and with non-B acute lymphoblastic leukemia in the five Nordic countries. By January 1994, 315 children had suffered at least one relapse. The bone marrow was involved in 216 cases. There were 69 isolated CNS relapses, 25 isolated testicular recurrences and five relapses in other extramedullary sites.

Of the 315 children with relapse, 94 are still in a second complete remission 12–138 (median: 78) months after relapse. The overall probability of a second event free survival (*P*-2.EFS) and survival after relapse was 0.28 and 0.33 respectively. The probability of remaining in second remission at 11 years was significantly correlated to the duration of first remission ($P < 0.001$), the site of relapse ($P < 0.001$) and gender ($P = 0.004$). The *P*-2.EFS for early, intermediate, and late bone marrow involved relapses were 0.08, 0.19, and 0.50 respectively. For early, intermediate and late isolated CNS relapses the *P*-2.EFS were 0.21, 0.38 and 0.61, respectively.

The *P*-2.EFS for boys with isolated testicular relapses was 0.69. Girls with isolated CNS relapse ($P < 0.001$) and with bone marrow involved relapse ($P = 0.04$) had a significantly better prognosis than boys.

Children with initial high risk criteria, especially T-ALL and mediastinal mass who relapsed, had a very poor prognosis. Conclusion: In this population-based study, about 30% of children with ALL obtained a long second remission and possible cure.

Key words: ALL, children, outcome after relapse, gender

INTRODUCTION

The introduction of multidrug combination chemotherapy for the treatment of acute lymphoblastic leukemia (ALL) has led to continuous complete remission (CCR) rates of 50–70%. Various factors at the time of diagnosis, especially the white blood cell count (WBC), age, chromosomal translocations, T-cell ALL, and gender may influence the chance of long-term remission. However, a number of children will relapse, after which the chance of ultimate survival and cure is greatly reduced.

Of the previous reports on survival after relapse of childhood ALL, only one study has been population-based [1,2]. Moreover, studies have included relatively few children, and the follow-up interval after relapse has been relatively short [1–4].

This report describes the chance of remaining in second CR after first relapse in a population-based study of 315 children over 12 months of age with non-B ALL treated in the five Nordic countries over a 5-year period. The purpose has been to identify factors which determined the length of the second remission.

MATERIALS AND METHODS

This study comprised all 809 children aged 1–15 years who were diagnosed with non-B ALL in Denmark, Finland, Iceland, Norway, and Sweden between July 1, 1981 and June 30, 1986. According to the common Nordic criteria, the children were divided into three risk groups (Table I) [5]. The number of children at standard

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TABLE I. Risk Criteria for Children With Non-B-ALL Over 1 Year Old

Group	Criteria
High risk (HR)	WBC $>50 \times 10^9$/l and/or CNS involvement and/or Mediastinal mass and/or T-cell ALL
Intermediate risk (IR)	No HR criteria Age 2–<10 years and WBC 21–51 $\times 10^9$/l From July 1984 WBC 10–51 $\times 10^9$/l Age <2 years or ≥10 years and WBC ≤50 $\times 10^9$/l
Standard risk (SR)	No IR/HR criteria Age 2–<10 years and WBC ≤20 $\times 10^9$/l From July 1984 WBC <10 $\times 10^9$/l

risk (SR) was 367, at intermediate risk (IR) was 224, and at high risk (HR) was 218 children. The distribution of the various risk factors in all patients is seen in Table II.

Initial treatment was stratified for risk group. In almost all SR children remission was induced with vincristine and prednisolone, and doxorubicin (Finland and Sweden) or asparaginase (Denmark, Norway, and Iceland). In July 1984, asparaginase was added to the induction treatment in Finland and Sweden. CNS prophylaxis was performed with three 24-hour infusions of methotrexate 0.5 or (after July 1984) 1.0 g/m^2 and eight intrathecal doses of methotrexate. The maintenance therapy included oral daily 6-mercaptopurine and weekly oral methotrexate until 36 months after diagnosis. No reinduction was given. In a pilot study, doxorubicin was not used during induction, but intravenous MTX infusions were added to the maintenance therapy during the first year of treatment. In most of the IR children the induction, consolidation, and CNS-prophylaxis was similar to that of the SR group. From July 1984, children with WBC 10–20 $\times 10^9$/l were "upgraded" from the SR to the IR group. In the IR children, maintenance therapy was intensified by pulses of vincristine and prednisolone with or without doxorubicin or MTX infusions during the first year. HR children were treated according to various protocols primarily based on the intensive regimens of Riehm, Wollner or Seip, or bone marrow transplantation after achieved first remission [5,6].

Of the 561 children with SR or IR ALL who obtained remission, 19 patients had CNS irradiation as part of the initial CNS directed therapy. Of 218 children with initial HR ALL, 123 had cranial irradiation as part of the ALL treatment. The 34 children with CNS leukemia at diagnosis had initially biweekly intrathecal injections of methotrexate until CNS remission; cranial irradiation was given to all of the children during the consolidation treatment.

Of the 809 children, 771 obtained an initial remission (95%). At 12.5 years the estimated event free survival (*P*-EFS) was 57, 55, and 47% for children with SR, IR, and HR ALL, respectively.

Bone marrow relapse was diagnosed when there were more than 5% blasts in the bone marrow. CNS involvement both at diagnosis and at relapse was defined as unequivocal blasts in a cytospin of the spinal fluid and more than 5 $\times 10^6$/l of mononuclear cells. Testicular relapse was diagnosed by blasts in a fine-needle aspiration or in a surgical biopsy.

By January 1994, 315 patients with relapses had been diagnosed. The bone marrow was involved in 216 cases of which 158 were isolated BM-relapses, and the remaining BM-combined relapses. From this study the percentage of blasts in the bone marrow at relapse could not be reported. There were 69 isolated relapses in the CNS, 25 isolated testicular relapses, and five recurrences in other extramedullary sites (Table III).

No uniform reinduction therapy was used, but relapse therapy was more intensive than first line treatment. Almost all children with CNS relapse who had not received CNS directed irradiation during first remission were treated with craniospinal irradiation.

The exact percentage of children who obtained second remission was not reported by the individual centers. However children who were alive and free of any secondary relapses three months from the time of the first relapse were considered to have achieved a second remission. Event free survival (EFS) was defined as survival in second complete remission.

Sixty-five children had a bone marrow transplantation (BMT), 46 children had an allogeneic BMT, and 19 children an autologous BMT as part of the relapse treatment. The decision to perform BMT was made by the individual centers. Table III shows the distribution of the 65 transplanted children among the various types of relapses.

All children were followed up annually for 1) continuous complete remission, 2) site and time of new relapse, 3) death and cause of death.

The latest follow-up was in January 1994, 90–150 months after initial diagnosis. The median time of observation after relapse for those who are alive in second remission is 78 months (range: 12–138 months). No patient has been lost from the follow-up.

Statistical analyses were performed with SPSS statistical software [7]. Important prognostic factors were identified by the backward elimination method using Cox's multiple proportional hazard regression model [8]. The factors included in the model were: year of diagnosis, country, age (1–<2 years, 2–<5 years, 5–<10 years, and ≥10 years at diagnosis), gender, white blood cell count, hemoglobin concentration, platelet count, T- or non-T cell ALL, mediastinal mass, or CNS leukemia at diagnosis, duration of first remission (months) and localisation of relapse (BM ± other sites, CNS isolated, testis

TABLE II. Initial Patient Characteristics

	Girls	Boys	Total	*P* values ♀/♂
Number	381	428	809	
P EFS	0.61 ± 0.03	0.48 ± 0.02	0.54 ± 0.02	<0.001
Age				
1–<2 years	23	30	53	
2–<10 years	297	318	615	
≥10 years	61	80	141	
WBC				
<10	213	210	423	
10–20	46	57	103	
20–50	64	64	128	
50–100	35	47	82	
>100	23	50	73	
T-ALL	20	46	66	
Mediastinal mass	17	47	64	
CNS leukemia	10	24	34	
Standard risk (SR)	189	178	367	
P-EFS	0.59 ± 0.04	0.54 ± 0.04	0.57 ± 0.03	N.S.
Intermediate risk (IR)	109	115	224	
P-EFS	0.59 ± 0.05	0.51 ± 0.05	0.55 ± 0.03	N.S.
High risk (HR)	83	135	218	
P-EFS	0.67 ± 0.05	0.36 ± 0.04	0.47 ± 0.03	<0.001

TABLE III. Outcome of the 315 Children After First Relapse

Site of first relapse	Duration of first remission	First relapse no.	No. second CCR (*P*-2.EFS)	No. alive (*P*-survival)	BMT No.[a]	
					Allo	Auto
BM relapse	<24 mo	114	9 (0.08)	9	17 (4)[b]	1 (0)
	24–36 mo	42	8 (0.19)	8	9 (3)	3 (2)
	>36 mo	60	32 (0.50)	40	10 (8)	9 (7)
Total		216	49 (0.21)	57 (0.23)	36 (15)	13 (9)
CNS relapse	<24 mo	32	7 (0.21)	10	3 (2)	1 (0)
	24–36 mo	21	8 (0.38)	10	1 (0)	1 (1)
	>36 mo	16	10 (0.61)	14	3 (3)	0 (0)
Total		69	25 (0.37)	34 (0.44)	7 (5)	2 (1)
Testes	<24 mo	5	2 (0.40)	2	1 (1)	1 (0)
	24–36 mo	4	2 (0.38)	3	0 (0)	2 (1)
	>36 mo	16	14 (0.87)	16	1 (1)	1 (1)
Total		25	18 (0.69)	21 (0.82)	2 (2)	4 (2)
Other sites		5	2 (0.30)	3	1 (0)	0 (0)
Total		315	94 (0.28)	115 (0.33)	46 (22)	19 (12)

[a]Patients treated with allogeneic (allo) or autologous (auto) bone marrow transplantation.
[b]Denotes surviving patients after BMT.

isolated, other sites). Life tables were performed using the Kaplan-Meier method. The distribution of P-2.EFS for different subgroups were compared via the Wilcoxon-Gehan test without adjusting for other prognostic factors [9]. The limit for significance was 0.05 in all analyses.

RESULTS

Of the 315 patients with relapse, 94 children are still in second complete remission for a median of 78 months (range: 12–138 months). The overall probability of second event free survival (*P*-2.EFS) is 0.28 ± 0.03, 11 years after relapse (Fig. 1). This figure also shows that the survival curve is rather similar to the curve for 2.EFS.

The *P*-2.EFS for children with bone marrow involved relapse, isolated CNS relapse, and isolated testicular relapse were 0.21 ± 0.03, 0.34 ± 0.06, and 0.69 ± 0.10, respectively (Fig. 2). In the Cox analyses the most important prognostic factor for *P*-2.EFS was the site of first

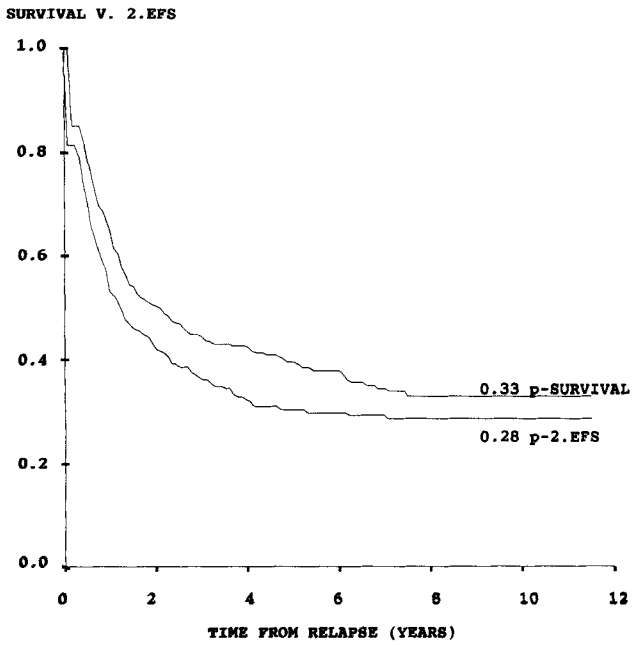

Fig. 1. Probability of second event free survival (*P*-2.EFS) and survival (*P*-SURVIVAL) in all 315 children with ALL after first relapse.

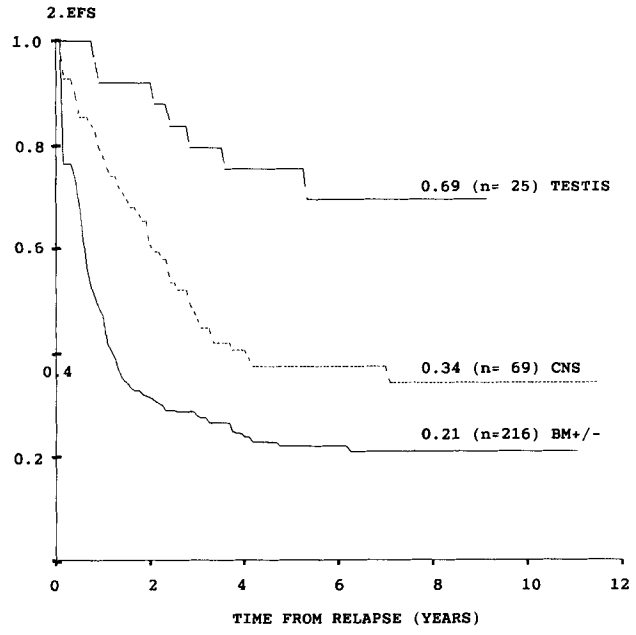

Fig. 2. *P*-2.EFS of children with bone marrow involved relapse (BM ±), isolated CNS relapse (CNS) and isolated testicular relapse (TESTIS).

relapse ($P < 0.001$), followed by the duration of first remission ($P < 0.001$) and gender ($P = 0.002$). There was no difference in outcome for children with isolated BM relapse compared with those with combined BM relapse (*P*-2.EFS: 0.21 and 0.23, respectively).

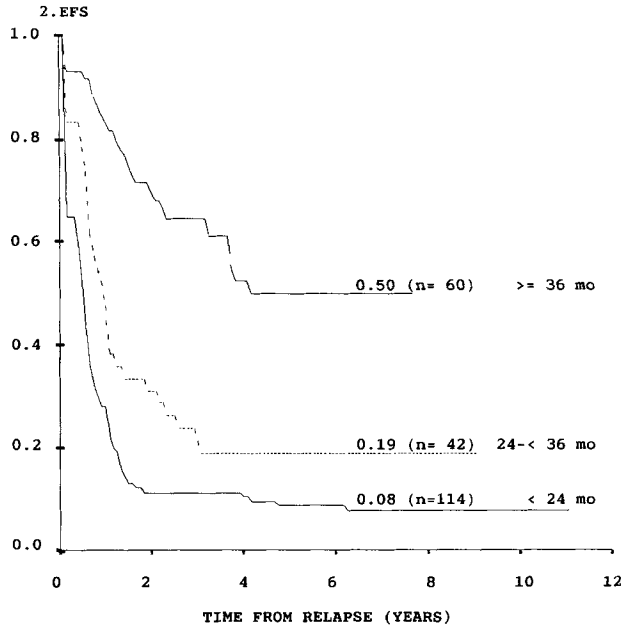

Fig. 3. *P*-2.EFS for 216 children with bone marrow involved relapses according to length of first remission.

There was also a significant association between the duration of 1. remission and the *P*-2.EFS for relapses involving the bone marrow (Fig. 3). The prognosis for patients both with early (<24 months after diagnosis) and intermediate relapses (24–<36 months after diagnosis) was poor. Children experiencing late relapses (≥36 months after initial diagnosis) had a high probability of remaining in the second remission (0.50 ± 0.08). There were statistically significant differences between *P*-2.EFS for children with late relapse compared to either early or intermediate relapse ($P < 0.001$), and between early and intermediate relapses ($P < 0.001$).

After isolated CNS relapse the *P*-2.EFS for early, intermediate, and late relapses were 0.21 ± 0.10, 0.38 ± 0.10 and 0.61 ± 0.13, respectively (Fig. 4). The difference between late and the combined group of early and intermediate isolated relapses was statistically significant ($P = 0.006$).

Of the 25 boys with isolated testicular relapses, 16 were late relapses. The *P*-2 EFS was 0.69 ± 0.10 (Fig. 2). Of the 16 boys with late relapses, 14 are still in the second CR (Table I).

There was no significant difference in outcome between girls and boys in the entire group of children with relapses ($P = 0.082$) (Table IV). However girls with an isolated CNS relapse fared better than boys ($P < 0.001$) (Fig. 5). But also when only bone marrow involved relapses were considered, the girls had a higher *P*-2.EFS than the boys ($P = 0.04$). This difference was more pronounced when the isolated testicular relapses were excluded from the analysis ($P = 0.004$).

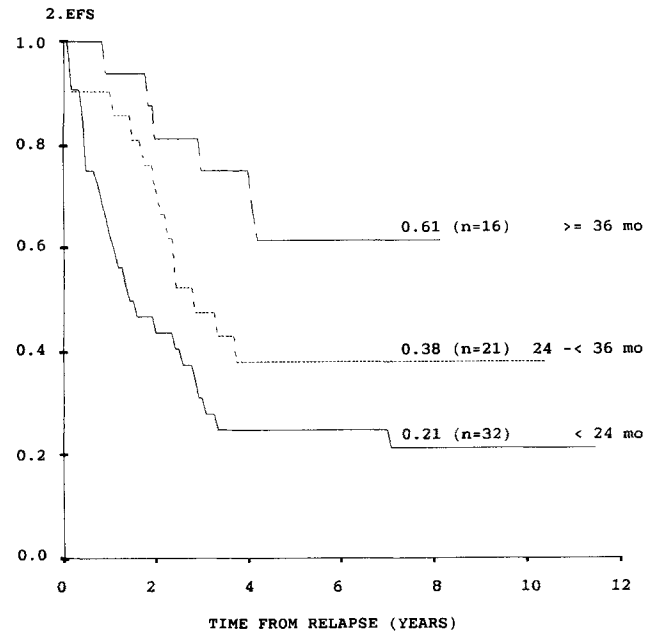

Fig. 4. *P*-2.EFS for 69 children with isolated CNS relapses according to length of first remission.

The *P*-2.EFS for children with initial high risk was significantly ($P < 0.001$) lower than that of the children with initial standard and intermediate risk criteria (data not shown). It was particularly children with high risk criteria such as initial T-ALL and mediastinal mass who had a low survival. Of 19 children with initial T-ALL who relapsed, all have died after relapse. Of 22 children with initial mediastinal mass who relapsed, only one is alive.

DISCUSSION

This study of an unselected population of 315 children with relapsed ALL showed that the probability of prolonged second remission was 29%, 10 years after relapse. The curve for 2.EFS reached a plateau at about 7 years after relapse. This figure compares favorably with an EFS of 31% at 6 years reported by the BFM group [4]. In that study children were generally treated more intensely both at initial diagnosis and at relapse than in the present study.

Like other studies [1,3,4,10,11] we also found that the duration of first remission was a significant parameter for the probability of long term second remission. The *P*-2.EFS for early bone marrow relapse in our study was lower than that of the BFM study which may be a result of a generally more intensive reinduction treatment used in the BFM study [4] for this group of relapsed children. However, in children with late relapse, the present study showed that more than half of these children remained in 2. remission, which compared favorably with the German and Dutch [4,1] results. The relatively favorable outcome after late bone marrow involved relapse may reflect the fact that initial treatment in this group of children, who mainly belonged to the standard or intermediate risk groups, had been too weak and that reinduction therapy accordingly, had a greater chance of salvage. Reinduction therapy varied to such an extent that the effect of individual treatment schedules could not be evaluated.

Bührer et al. [12] reported a better outcome for children with combined bone marrow relapses as opposed to children with isolated bone marrow relapses. This difference disappeared after allogeneic BMT and these patients were censored from the life table analyses at the time of BMT. In our material the incidence of allogeneic BMT was similar to that reported by Bührer et al., and we did not censor patients at the time of BMT. Furthermore, since the definition of bone marrow relapse was the occurrence of >5% (and not 25% for isolated bone marrow relapse) blasts in the bone marrow irrespective of extramedullary relapse, we might have treated more patients with an early isolated bone marrow relapse who had a small tumor load. These conditions might explain why we did not detect any difference in outcome between isolated and combined bone marrow relapses.

This study also confirms previous observations that children with isolated extramedullary relapse fared better than when the relapse included the bone marrow. After CNS relapse the probability of 2. EFS 11 years after relapse in our study was comparable to the results of POG [13]. However, the initial CNS directed therapy is important for outcome after CNS relapse. Most of our children had not received cranial irradiation for initial CNS prophylaxis. This may have contributed to a higher "salvage rate" after isolated CNS relapse as compared with a group of children who all had prophylactic CNS irradiation [14]. In that study a very low CNS-involved relapse rate was reported probably because of cranial irradiation to all children irrespective of risk group. However a significant amount of sequelae caused by the cranial irradiation (18–28 Gy) may be expected. Accordingly, the Nordic countries are currently using 5 gr/m^2 methotrexate infusions with intrathecal MTX for about 90% of children with ALL, restricting cranial irradiation only to children >5 years and with high risk ALL at diagnosis.

The EFS curves reached a plateau between 5 and 7 years after 1. relapse, therefore at least 10 years of observation from the time of initial diagnosis is necessary in order to evaluate the chance of ultimate survival because the course of disease in children with late isolated extramedullary relapses may be very long.

Girls with ALL may have a better chance of long term initial event free survival compared with that of boys which particularly has been shown in earlier studies [11,13,15–17]. This has also been demonstrated for girls

TABLE IV. Patient's Gender as a Prognostic Factor After Relapse of ALL

Localization of relapse	Sex	Number	$P-2.EFS \pm SE$	P value
All relapses	Females	118	0.37 ± 0.04	0.082
	Males	197	0.23 ± 0.03	
Bone marrow	Females	94	0.27 ± 0.05	0.04
	Males	122	0.16 ± 0.04	
CNS isolated	Females	22	0.73 ± 0.10	< 0.001
	Males	47	0.14 ± 0.07	
All relapses, excluding testes	Females	118	0.37 ± 0.04	0.004
	Males	172	0.15 ± 0.03	

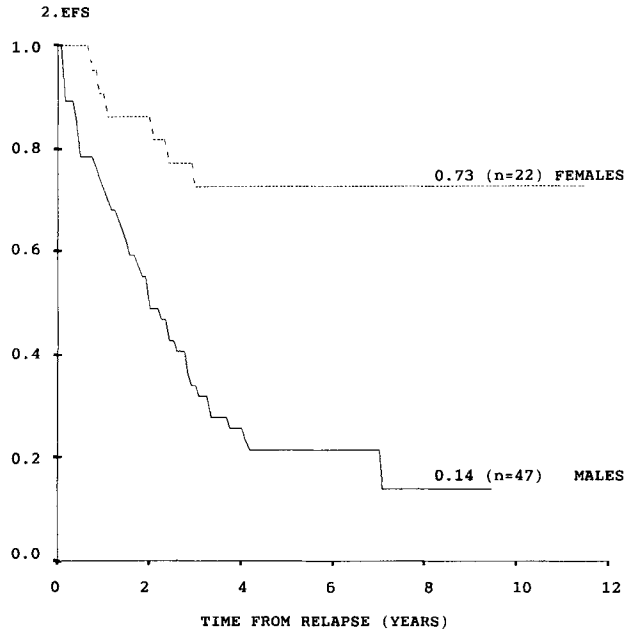

Fig. 5. P-2.EFS of 69 children with isolated CNS relapse according to gender.

with high risk ALL in a Nordic study [18]. The present study showed that even after relapse, there was a significant difference in the chance of long term second EFS favoring the girls. This finding has also been observed by Behrendt et al. [2] but not in the POG study [13]. If these findings are repeated in the intensified future treatment protocols in the Nordic countries, gender may have to be considered in the risk stratified treatment modality.

The purpose of this study was not to evaluate the role of BMT. It is seen, however, from Table I that 11 of the 18 children remaining in 2. CRR after early and intermediate BM relapse had been transplanted. This indicates that allogeneic BMT is an especially important treatment modality in these situations as concluded in the BFM studies [19].

A population-based study of the effect of therapy after relapse of childhood ALL is warranted. Future relapse protocols should probably be stratified for sex, length of initial remission, and localization of relapse.

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