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Research Paper

EFFICACY OF AN INTENSIVE POST-INDUCTION CHEMOTHERAPY
REGIMEN FOR ADULT PATIENTS WITH PHILADELPHIA CHROMOSOME-
NEGATIVE ACUTE LYMPHOBLASTIC LEUKEMIA, GIVEN
PREDOMINANTLY IN THE OUT-PATIENT SETTING

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Running title : Therapy for ALL on an out-patient basis

ABSTRACT

Intensification of chemotherapy in adults with acute lymphoblastic leukemia (ALL) has improved outcome. The aim of this analysis was to evaluate outcome of patients treated with an intensive regimen based on that used in the German national trials, but adapted in order to enable treatment to be given mainly on an Out-patient basis, once complete remission (CR) had been achieved. Between 2000 and 2007, 53 patients with Philadelphia chromosome-negative ALL (40 with B-ALL and 13,T-ALL) received treatment. Complete remission (CR) was achieved in 47/53 (89%), with no significant difference in CR rate between B and T-ALL. At a median follow-up of 6.3 years, 25 patients are alive, 23 (43%) in 1st CR, twenty have relapsed. No patient died in CR due to treatment-related toxicity. At 5 years, overall survival was 50% and disease-free survival, 53%. Thirty-four of the 47 patients in whom CR was achieved completed therapy and are evaluable for duration of hospital stay and number of Day Unit attendances. The median time in hospital during the year of treatment was 10 weeks (range 6-44) with no significant difference between patients \leq vs >30 years old. It was possible to administer this intensive protocol largely on an Out-patient basis without compromising patient safety.

Key words:

adult acute lymphoblastic leukemia (ALL), intensive chemotherapy, Out-patient setting, overall survival

Introduction

The outcome of patients with acute lymphoblastic leukemia (ALL) has improved with intensification of therapy. Complete remission (CR) can now be achieved in the majority of adults with ALL but only 30-40% are cured, the proportion varying according to well-described clinical and biological risk factors [1-9]. In recent years, two main consolidation strategies have been used to try and improve outcome: intensive chemotherapy programmes, reserving allogeneic SCT for patients with Philadelphia chromosome (Ph)-positive ALL (Ph+ALL), or allogeneic stem cell transplantation (SCT) for all patients in first CR with a sibling donor. Whilst some studies have shown equivalent outcomes for the two latter approaches [10,11], others have demonstrated better results in specific subgroups of patients receiving an allograft [12-14]. The cooperative MRC/ECOG trial showed better overall survival with SCT in patients with standard risk ALL but failed to prove superiority for SCT in the high risk category, due to a high treatment-related mortality (36% at 2 years) [13].

In view of the impressive results achieved in Germany using an intensive, sequential chemotherapy protocol given over twelve months [15], in September 2000, a modified version of the GMALL 06/99 protocol was adopted at **St. Bartholomew's Hospital**. The aim of this analysis was to evaluate the outcome of patients receiving this regimen, which includes the use of gram doses of cyclophosphamide and methotrexate. The original protocol was modified as follows: **standard-dose** cytarabine was given subcutaneously instead of intravenously, (equivalence having been demonstrated in terms of the blood levels achieved [16]) obviating the need for hospital attendance, let alone admission. Furthermore, gram doses of cyclophosphamide and methotrexate were given in the Day Unit, rather than patients being admitted. Gram-dose Methotrexate **was followed by folinic acid: 30 mg orally, every 6 hours, for a total of 6 doses.**

Design and Methods

Patients

Between September 2000 and June 2007, 53 consecutive, newly diagnosed patients aged between 15 and 70 years with Ph-negative B- or T-lineage ALL (excluding mature B-ALL), received the modified 'GMALL' protocol. Signed, informed consent for treatment was required. The diagnosis was based on morphological examination of bone marrow (BM) and peripheral blood and on flow cytometric immunophenotyping. Standard cytogenetic analysis was performed to complete the diagnostic profile.

Patients with the following risk factors: pro-B ALL, pre-B ALL with WBC $\geq 30 \times 10^9/L$, early or mature T or thymic T ALL with WBC $\geq 100 \times 10^9/L$ and ALL with an *MLL* rearrangement, were defined as being at 'high risk' (HR) for recurrence [4]. All other patients were designated 'standard risk' (SR). Clinical characteristics are shown in Table 1. Based on risk factors, 24 patients (45%) had 'HR' ALL and 29 (55%) 'SR' disease.

Treatment

Treatment Strategy: Treatment continued for 12 months. Following initial admission for diagnosis and administration of remission induction therapy, once the neutrophil count had recovered to $0.5 \times 10^9/l$, patients were treated as much as possible on an Out-patient basis, attending the Hemato-Oncology Day Unit at SBH, twice or thrice weekly.

The standard doses of cytarabine were administered by the patient, a trained relative, or by a District Nurse. Methotrexate (1.5 g/m^2) followed by oral leucovorin rescue and cyclophosphamide (1 g/m^2) were given on the Day Unit, each over a period of 1 hour, with stringent attention to hydration. Thus, unless there was a specific contra-indication, patients who lived within 45 minutes' drive from the hospital were able to be at home for a substantial

proportion of the 12 months. They were of course always admitted immediately in the event of a problem, admission for intravenous antibiotics being mandatory for symptoms and/or signs of sepsis in the presence of neutropenia (defined as neutrophils $< 1.0 \times 10^9 /l$).

In contradistinction to the original protocol, it was decided *a priori* that no patients would electively have an allograft in 1st remission, (those with Ph+ve ALL being treated according to a different protocol). The treatment strategy was also not based on evaluation of 'minimal residual disease'.

Treatment details are shown in Figure 1. Remission induction chemotherapy consisted of 2 blocks, the first comprising: dexamethasone, vincristine, daunorubicin and PEG-asparaginase given over 3 weeks, followed by a second 3-week cycle comprising cyclophosphamide, cytarabine and 6-mercaptopurine (6-MP). Consolidation therapy consisted of 6 cycles, four of which included gram doses of methotrexate and one, high-dose cytarabine, over a period of 44 weeks, with two re-induction blocks, at weeks 22 and 24. G-CSF was given throughout to maintain the neutrophil count at $\geq 1 \times 10^9 /L$ in order to reduce treatment delays and the risk of infection. Central nervous system (CNS) prophylaxis was given in both T and B-lineage ALL and comprised 4 intrathecal (IT) injections of methotrexate and '5 triple IT' injections, followed by cranial irradiation (18 Gy) on completion of chemotherapy (weeks 52-56). A standard maintenance therapy with 6-mercaptopurine and methotrexate for 2 years was administered only in patients with B-lineage ALL. Patients with T-ALL did not receive any maintenance.

Response criteria

A bone marrow aspirate was performed on day 24. At this point, the blood count invariably showed profound cytopenia, and the bone marrow was virtually always hypocellular with no leukemic blast cells. On recovery of the count (to levels compatible with the definition of CR), the bone marrow was repeated (to document CR) and the next cycle of treatment started. In

patients in whom the bone marrow at day 24 showed >30% blasts, the second induction cycle was given irrespective of the blood count, if the patient was otherwise well enough to continue treatment.

Complete remission was defined as a morphologically normal marrow with less than 5% blasts, when the Hb > 10g/L, neutrophils > 1×10^9 /L and platelets > 100×10^9 /L.

Refractory ALL was defined as persistent leukemia following two cycles of induction chemotherapy.

Early death was defined as death during induction before treatment response had been assessed and *relapse* as recurrence of disease following achievement of CR. Relapses were further classified as isolated to BM (> 5% blasts), isolated to the CNS, or 'combined' (recurrence in BM and CNS concurrently).

Statistical analysis

Overall Survival (OS) was measured from the date of diagnosis to the date of death or last follow-up. *Disease-free survival* (DFS) was calculated from the date of CR to the date of relapse or death in CR from any cause and was censored at last follow-up. *Remission Duration* (RD) was calculated from the date of CR to the date of relapse or last follow-up. Actuarial survival analysis was performed according to the method described by Kaplan and Meier and the curves compared by the log-rank test. Differences in response rate across patient subgroups were compared by the χ^2 statistic.

Results

Response to treatment

CR was achieved in 47/53 patients (89%), with no significant difference in CR rate between B- and T-ALL. There were three early deaths from infection and three patients had refractory disease. Age ≥ 35 years was the only significant factor associated with a lower probability of achieving CR ($p=0.004$). No statistically significant difference in CR rate was observed between SR and

HR groups (27/29 v 20/24, respectively, $p=0.39$). CR was achieved in all 4 patients with an *MLL* rearrangement.

Survival

At a median follow-up of 5.5 years (range 2.5 – 8.5), 25/53 patients are alive (47%), twenty-three (43%) in 1st CR. Three patients died after >4 years in CR, two from secondary myelodysplasia and one who tragically took his own life. The estimated 5-year OS was 50% and did not differ significantly between patients with SR ALL (52%) and HR ALL (48%) risk ($p=0.4$) (Figure 2). There was likewise no statistically significant difference in OS or DFS between patients who presented with unfavorable cytogenetics and those with favorable/intermediate cytogenetic abnormalities (data not shown). Six of the 21 patients who developed recurrent disease (see below) are alive.

Remission Duration

Recurrence occurred in 21/47 patients overall, one month to 6 years following achievement of CR. The median remission duration was 6 years (range 0.1-8 years) (Fig. 3). Fourteen patients relapsed in BM alone (at 0.5–6 years), four had an isolated CNS relapse (at 0.3-1.4 years) and three developed recurrent leukemia concurrently in the BM and CNS. Three of the seven patients who developed recurrent leukemia in the CNS had T- ALL. At 1st recurrence, 15/21 patients were re-treated with curative intent, 2nd CR being achieved in 8/15. Four went on to receive an allogeneic SCT but only one of the latter is alive (at 7.3 years). Two of the four patients with an *MLL* rearrangement developed recurrent leukemia; two subsequently died, two remain well in 1st CR.

The estimated 5-year disease-free survival (DFS) was 53%, ranging from 57% in SR ALL to 48% in the HR ALL ($P=0.5$) (Figure 4). There was a trend towards better DFS in patients with T-lineage ALL, with an estimated DFS of 60% at 5 years, compared with 50% in B-lineage ALL ($p= 0.39$).

Induction and post-induction results are summarized in Table 2.

Duration of hospital stay

Thirty-four of the 47 patients in whom CR was achieved completed the planned therapy and are thus evaluable for assessment of duration of in-patient stay and number of Day Unit attendances over the 12-month period. Thirteen patients were unable to complete therapy (8 due to unacceptable clinical toxicity, and 5 because of recurrence whilst on treatment). The median total duration of in-patient stay was 10 weeks (range 6-44), made up of the initial 4 weeks, and subsequent admissions for those parts of the protocol that required the patient to be in hospital and admissions for treatment of neutropenic sepsis. There was no statistically significant difference in duration of in-patient stay between younger (≤ 30 years) and older patients (>30). The median number of Day Unit attendances was 20 (range 2-69). (The 'outlying' results relate to one patient who remained in hospital for virtually the whole time [44 weeks] and therefore attended the Day Unit only twice. She had multiple previous and concurrent medical problems, which in turn resulted in numerous complications. The person was therefore unable to complete the planned treatment, unfortunately developed recurrent leukemia and died).

Discussion

The intensive 'G-MALL' regimen was modified to enable treatment to be given mainly in the Out-patient setting. Doing so did not compromise the results overall, 50% of patients being alive at 5 years. These results are certainly not inferior to those achieved elsewhere [3-6,12-15,17] and have been achieved without resource to allogeneic stem cell transplantation in first remission. Moreover, they compare favorably with outcomes reported using the same regimen but given predominantly to patients in hospital [15].

Standard risk factors did not appear to influence outcome, whilst with regard to immunophenotype, relatively good results were achieved in the small group of patients with T-ALL (DFS 60% at 5 years). Amongst the factors that probably contributed to this favorable outcome, particularly in the patients with T-ALL was the use of 'gram doses' of cytarabine and cyclophosphamide, both known to be associated with better outcome in this subgroup [5,18,19]. It is somewhat unusual for cyclophosphamide and methotrexate to be given at gram doses in the Out-patient setting. In Germany, this protocol usually involves admission to hospital for prolonged periods of time (D. Hoelzer, personal communication). In the patients treated at SBH, the 'gram-dose' chemotherapy cycles were well tolerated and were not associated with any treatment-related deaths in CR.

The bone marrow recurrence rate was relatively low (17/47, 36%) in a population well balanced between standard and high risk patients. In contrast, the CNS recurrence rate was quite high (8.5%). The reasons for this are not clear, considering that the systemic chemotherapy included high-doses of CNS-penetrating agents. In particular, the administration of high-dose methotrexate over a period of one hour results in higher serum concentrations than prolonged infusion, with correspondingly higher concentrations in the cerebrospinal fluid. However, the dose of prophylactic cranial irradiation was relatively low, 18 Gy and the radiotherapy was delayed until completion of 12 months' chemotherapy. This prophylactic schedule was associated with an unacceptably high CNS relapse rate of 30% (3/10) in T-ALL. This could

perhaps be improved in this high-risk subset through the use of an earlier cranial irradiation and/or a greater exposure to systemic high-dose cytarabine or higher methotrexate doses.

In conclusion, this study has confirmed the reproducibility of the GMALL 06/99 protocol [4] modified for Out-patient administration in adult patients with ALL and has identified interesting possibilities for simplifying therapy, particularly for patients with standard risk ALL. It proved possible to administer this intensive protocol largely on an Out-patient basis, without compromising patient safety. The potential implications of the findings, for example, the use of *subcutaneous* cytosine arabinoside, able to be self-administered or given by a district nurse at home, if widely adopted, would have considerable impact if implemented generally.

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Authors' Contributions

TAL and AR are the principal physicians and take primary responsibility for the paper. TI and AR wrote the paper. TI, SK, AR and TAL were involved in the care of patients. FM and SK compiled the data. FM and TI analyzed the data. M.J. is responsible for the laboratory data. All authors reviewed the manuscript.

Conflict of interest

The authors report no conflicts of interest.

Legend

Figure 1. Modified GMALL treatment schema

Abbreviations: DNR: daunorubicin, ADR: adriamycin, VCR: vincristine, DEXA: dexamethasone, Peg-Asp: PEGylated asparaginase, CY: cyclophosphamide, 6-MP: 6-mercaptopurine, HD-Ara-C: high-dose cytarabine, HD-MTX: high dose methotrexate, VP-16: etoposide, VDS: vindesine, TG: thioguanine, VM26: teniposide, PRED: prednisolone, IT-MTX: intrathecal methotrexate, ITT: triple intrathecal injection, p.o: oral, i.v.: intravenously, s.c.: subcutaneously.

Doses and schedule:

Induction I and II: DEXA: 10 mg/m² (3 divided doses) p.o. days 1-5 and 11-14, VCR: 2 mg i.v. days 4,11,18, DNR: 45 mg/m² (30 mg/m² if age > 55 years) i.v. days 4,5,11,12, Peg-Asp: 1,000 U/m² (500 U/m² if age > 55 years) i.v. day 18, IT-MTX: 15 mg day 1. CP: 1,000 mg/m² i.v. days 24,44, ara-C: 75 mg/m² s.c. days 26-29, 33-36, 40-43, 6-MP: 60 mg/m² p.o. days 24-44, IT-MTX: 15 mg day 26,33,40.

Consolidation I: DEXA: 10 mg/m² (3 divided doses) p.o. days 1-5, VDS: 3 mg/m² (max 5 mg) i.v. day 1, HD-MTX: 1,500 mg/m² i.v. day 1, VP-16: 250 mg/m² i.v. days 4-5, HD-ara-C: 2,000 x 2 mg/m² i.v. day 5.

Consolidation II: HD-MTX: 1,500 mg/m² i.v. days 1,15, Peg-Asp: 500 U/m² i.v. days 2,16, 6-MP: 60 mg/m² p.o. days 1-7, 15-21.

Reinduction I and II: PRED: 20 mg/m² x 3 p.o. days 1-14, VDS: 3 mg/m² (max 5 mg) i.v. days 1,7, ADR: 50 mg/m² i.v. days 1,7, ITT (MTX:15 mg, ara-C: 40 mg, DEXA: 4 mg) day 1,15. CP: 1,000 mg/m² i.v. day 15, ara-C: 75 mg/m² s.c. days 17-20, 24-27, TG: 60 mg/m² p.o. days 15-28.

Consolidation III: HD-MTX: 1,500 mg/m² i.v. days 1,15, Peg-Asp: 500 U/m² i.v. days 2,16, 6-MP: 60 mg/m² p.o. days 1-7, 15-21.

Consolidation IV: ara-C: 150 mg/m² i.v. days 1-5, VM26: 100 mg/m² i.v. days 1-5, ITT day 1.

Consolidation V: CP: 1,000 mg/m² i.v. day 1, ara-C: 500 mg/m² s.c. day 1, ITT day 1.

Consolidation VI: HD-MTX: 1,500 mg/m² i.v. days 1,15, Peg-Asp: 500 U/m² i.v. days 2,16, 6-MP: 60 mg/m² p.o. days 1-7, 15-21.

G-CSF 5 µg/Kg s.c. from the end of each cycle until neutrophils > 1 × 10⁹/L.

ITT at week 52. Cranial irradiation 18 Gy at weeks 52-56.

Figure 2. Kaplan-Meier estimate of overall survival (OS) in **(A)** all treated patients and **(B)** according to risk category (SR: standard risk, HR high risk)

Figure 3. Kaplan-Meier estimate of duration of remission in all patients achieving first complete remission.

Figure 4. Kaplan-Meier analysis of Disease-Free Survival in **(A)** all patients and **(B)** according to risk category (SR: standard risk, HR: high risk)

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Table 1. Clinical characteristics at initial presentation

	Number (%)
Patients	53
<i>Gender</i>	
Male	34 (64)
Female	19 (36)
<i>Age, years</i>	
Median [range]	32 [16-70]
<i>Peripheral blood blast count</i> $\times 10^9/L$, median[range]	4.5 [0-849]
<i>Immunophenotype</i>	
<u>B-lineage</u>	40 (75)
proB/pre B	9/31
<u>T-lineage</u>	13 (25)
early/thymic/mature	5/5/3
<i>CNS involvement</i>	1 (2)
<i>Cytogenetics*</i>	
normal	17
del 9(p)	5
high hyperdiploid	3
t(8;14)**	1
low hypodiploid	1
MLL rearrangement	4
complex (≥ 5 unrelated clonal abnormalities)	3
del 6(q)	1
other	11
Not evaluable	7

CNS: central nervous system.

*According to Medical Research Council (MRC) and UKALLXII/Eastern Cooperative Oncology Group (ECOG) criteria, 'high risk' cytogenetics is defined by: t(8;14), MLL rearrangement, complex, low hypodiploid.^[7]

**an IgH re-arrangement was demonstrated by 'FISH' but there was no MYC re-arrangement

Table 2. Outcome to Therapy

Outcome to Induction therapy (N=53)		Subsequent outcome of patients entering CR (N=47)	
Complete Remission	47 (89%)	Alive in CR1	23 (49%)
No response	3 (5.5%)	Relapse	21 (45%)
Early Death	3 (5.5%)	Death in CR	3 (6%)

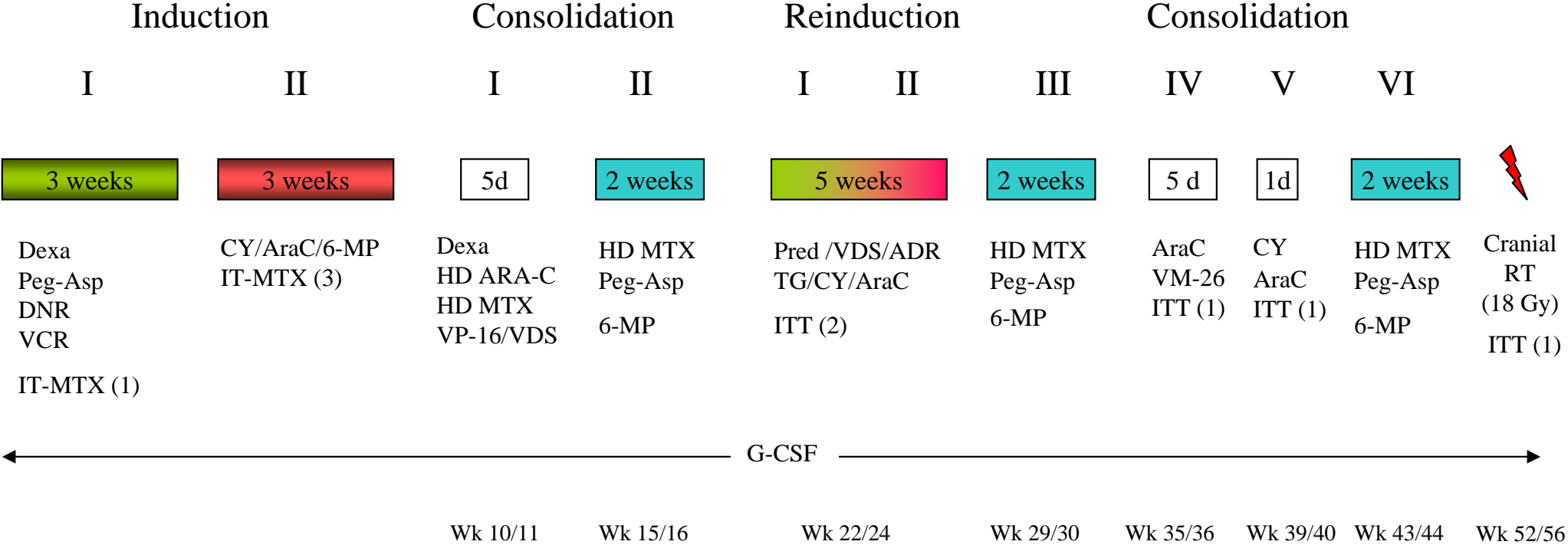


Figure 1. Treatment Schema

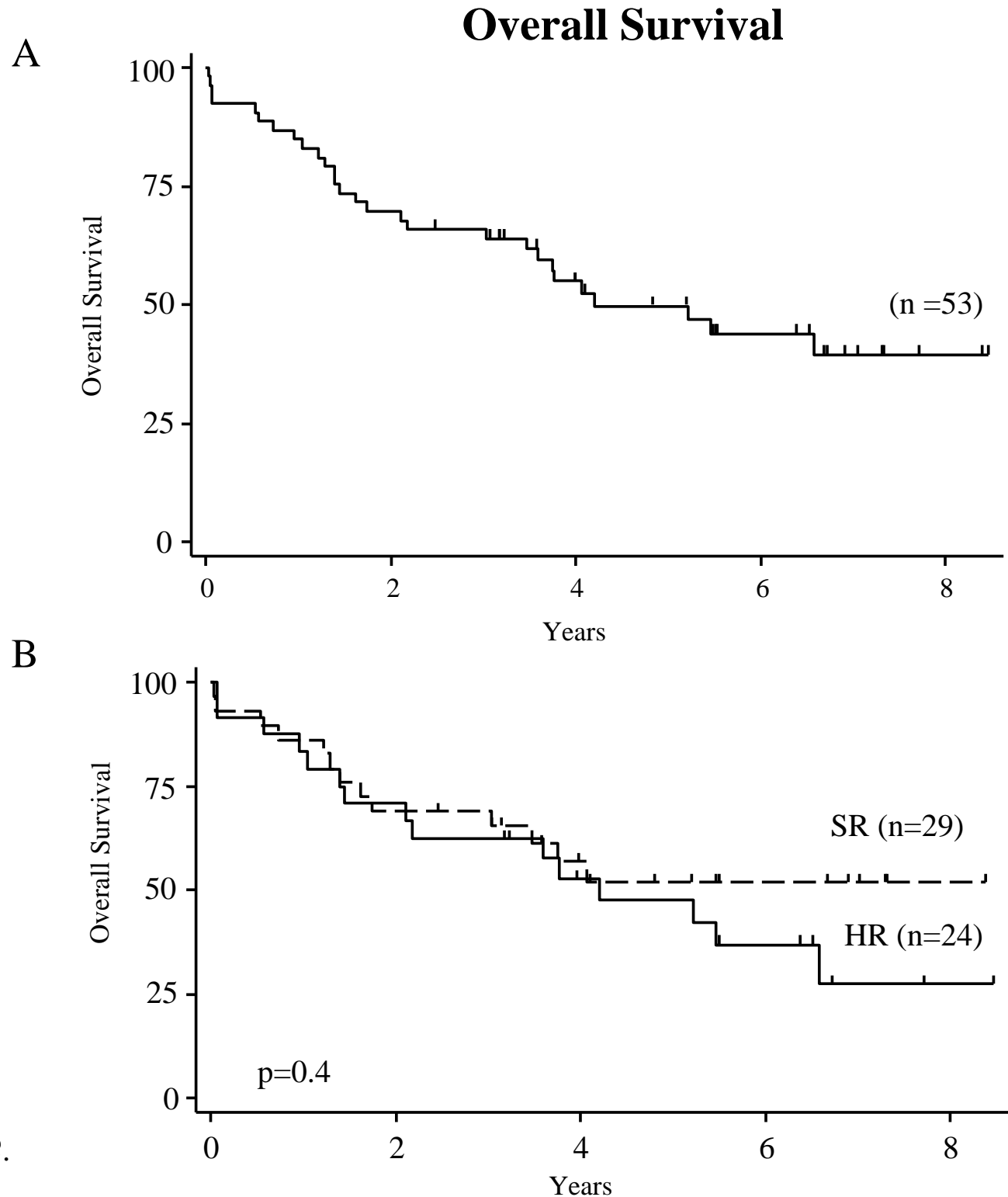


Figure 2.

Remission Duration

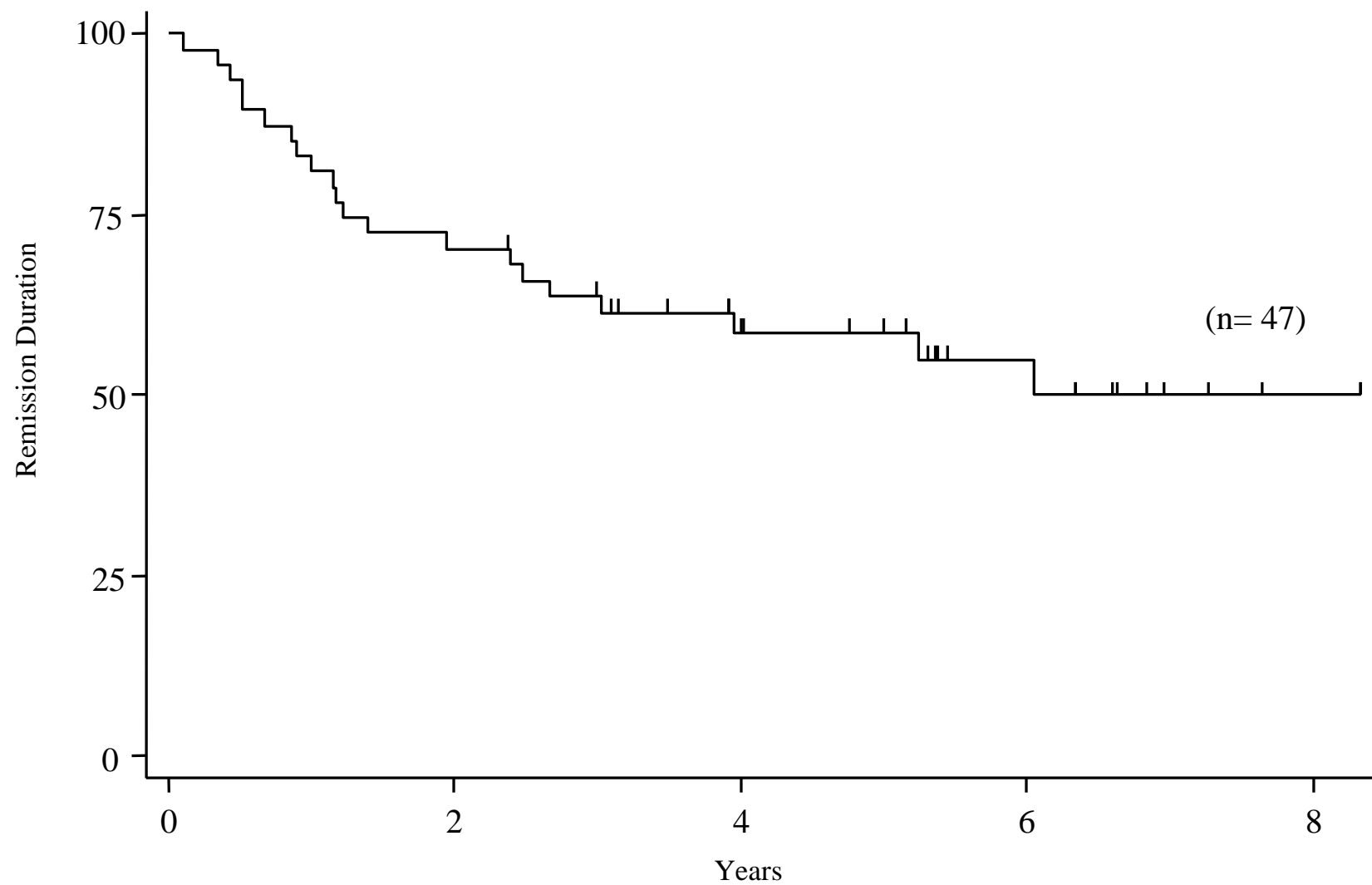


Figure 3.

Disease-Free Survival

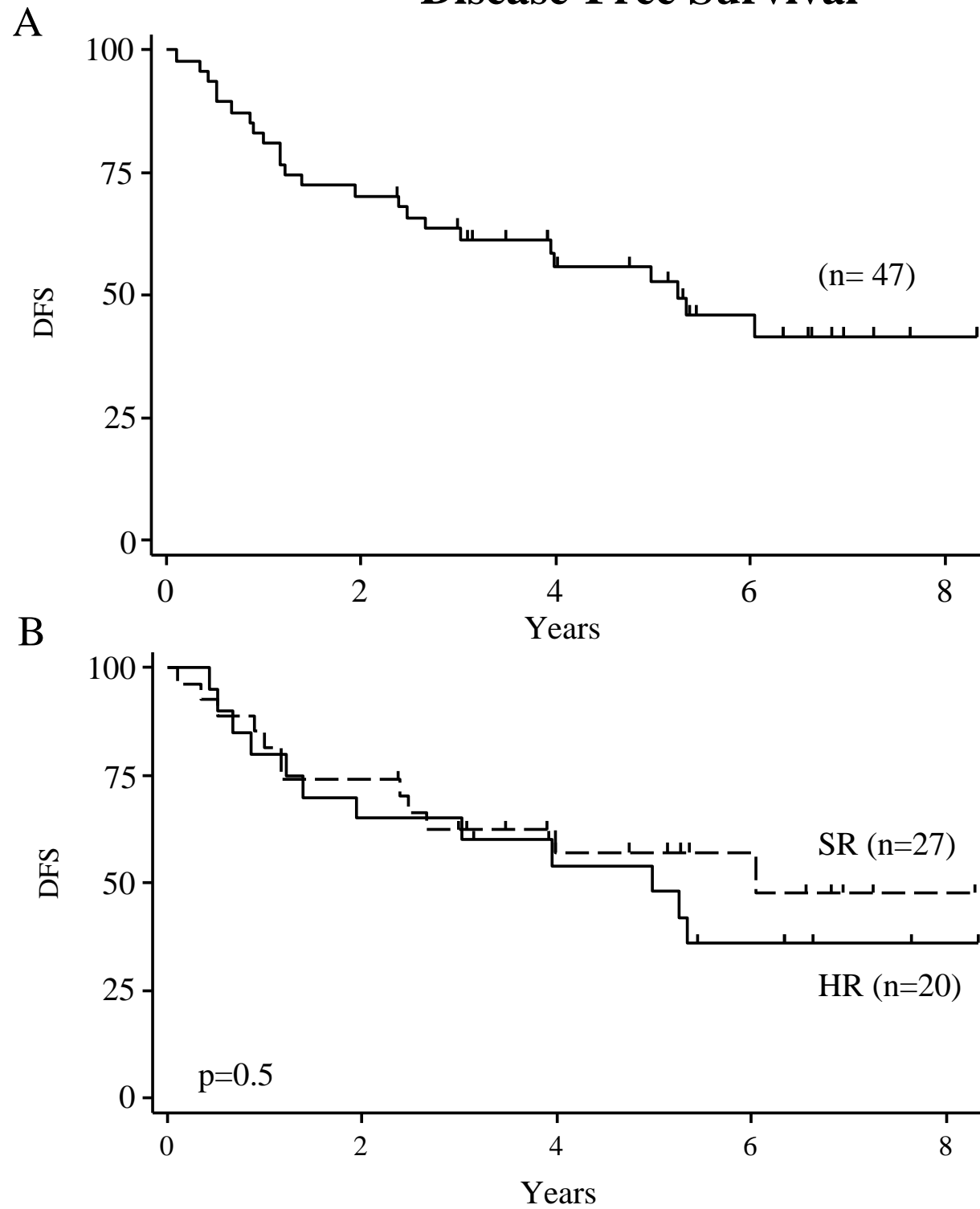


Figure 4.