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by Boris Labar, Stefan Suciu, Roel Willemze, Petra Muus, Jean-Pierre Marie, Georges Fillet, Zwi Berneman, Branimir Jaksic, Walter Fereman, Dominique Bron, Harm Sinnige, Martin Mistrik, Gerard Vreugdenhil, Robrecht de Bock, Damir Nemet, Caroline Gilotay, Sergio Amadori, and Theo De Witte

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Dexamethasone versus prednisolone for adult acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) patients - final results of the ALL-4 randomized, Phase III trial of the EORTC Leukemia Group

Boris Labar[1], Stefan Suciu[2], Roel Willemze[3], Petra Muus[4], Jean-Pierre Marie[5], Georges Fillet[6], Zwi Berneman[7], Branimir Jaksic[8], Walter Feremans[9], Dominique Bron[10], Harm Sinnige[11], Martin Mistrik[12], Gerard. Vreugdenhil[13], Robrecht De Bock[14], Damir Nemet[1], Caroline Gilotay[2], Sergio Amadori[15], and Theo de Witte[3] *on behalf of the EORTC Leukemia Group*

[1]*Department of Hematology, University Hospital Center Rebro, Zagreb, Croatia*
[2]*EORTCHeadquarters, Brussels, Belgium*
[3]*Dept. of Hematology, Leiden University Medical Center, the Netherlands*
[3] *Dept. of Hematology, St Radboud University Hospital, Nijmegen, the Netherlands*
[5]*Dept. of Hematology, Hotel-Dieu, Paris, France*
[6]*Dept. of Hematology, Liège, Belgium*
[7] *Dept. of Hematology, Antwerp University Hospital, Antwerp, Belgium*
[8] *Dept. of Hematology, Clinical Hospital "Merkur", Zagreb, Croatia*
[9] *Dept. of Hematology, Erasme Hospital, Brussels, Belgium*
[10]*Institute Jules Bordet, Experimental Hematology, Brussels, Belgium*
[11]*Dept of Hematology, Jeroen Bosch Ziekenhuis, S. Hertogenbosch, the Netherlands*
[12] *Clinics of Hematology and Transfusiology, University Hospital, Bratislava, Slovakia*
[13] *Dept. of Internal Medicine, Maxima Medical Center, Veldhoven, the Netherlands*
[14]*AkademischZiekenhuis, Middelheim, Antwerp, Belgium*
[15]*Hematology/Oncology Transplant Unit, University of Rome Tor Vergata, Rome, Italy*

Running title: Dexamethasone vs. Prednisolone for adult ALL/LBL

Key words: adult ALL, lymphoblastic lymphoma, dexamethasone, prednisolone, randomized trial.

Correspondence: Professor Boris Labar, Department of Hematology
University Hospital Center Rebro Kispatic street 12, 1000 Zagreb,
Croatia.
E-mail: boris.labar@inet.hr

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Introduction

Corticosteroids are the standard component for the treatment of acute lymphoblastic leukemia (ALL)and lymphoblastic lymphoma (LBL). The response to corticosteroids during the pretreatment phase is essential in defining the risk of ALL and treatment outcome, especially in children (1-3) . Corticosteroids are also part of the induction and the maintenance therapy in adults (4, 5). Dexamethasone (DXM) is 6.5 times more potent than prednisolone (PDN) as measured by conventional glucocorticoid activity, but it shows a 16 fold gain in potency against lymphoblasts in vitro, suggesting that dexamethasone might be a more active corticosteroid in the treatment of ALL (6-7). The better penetration in the central nervous system (CNS) (8) and the enhanced lymphoblastic cytotoxicity might explain the lower bone marrow relapse rate, the lower CNS relapse rate and the advantage in event-free survival in children receiving dexamethasone (9–11). The attempts to increase its antileukemic effect by increasing the dose of DXM has been associated with increased toxicity and early deaths mostly due to severe infections (12).

Since comparison of DXM versus PND is not available for adult patients with ALL/LBL we investigated in this randomized phase trial the antileukemic activity and toxicity of DXM compared with PDN.

Design, Patients and Methods

Previously untreated adult ALL or LBL patients were eligible to be entered in this trial. The study was approved by the EORTC Protocol Review Committee and by Ethic Committees of the participating institutions. The study was conducted in 20 European centers, in accordance with the Declaration of Helsinki. The study design is presented in Figure 1. Inclusion criteria were absence of prior malignancy except those originating in the skin (non-melanoma) or those considered to be cured, absence of severe cardiac, pulmonary, neurological or metabolic disease, adequate liver (bilirubin <2 mg/dl) and renal (creatinine <2 mg/dl) function tests (unless considered due to leukemic involvement), and HIV negativity. All participants gave their informed consent.

For remission induction patients were randomized to receive DXM or PDN together with chemotherapy. The first randomization was prospectively stratified by WBC, diagnosis (ALL vs. LBL), age (15-19,20-34,35-60, >60 years) and center using a minimization technique. Patients who achieved complete or good partial remission were eligible to receive a course of intensive consolidation with high dose cytarabine and mitoxantrone (HAM). All patients in complete remission (CR) after HAM consolidation underwent treatment with two courses of consolidation consisting of high dose methotrexate and asparaginase (MA). After MA consolidation patients 50

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Abstract

Background

Corticosteroids are the standard component for the treatment of ALL and LL patients. Our aim was to assess whether dexamethasone (DXM) result in a better outcome than Prednisolone (PDN).

Design and Metdhods

Adult ALL and LL patients were randomized to receive in induction on days 1-8, 15-22, either DXM 8 mg/m^2 or PDN 60 mg/m^2. Those who reached complete remission (CR), two courses of consolidation (HAM and MA) were administered. Subsequently patient younger than 50 years, with a donor, had to receive AlloSCT, whereas the others, either autoSCT or high dose maintenance chemotherapy with prophylactic CNS irradiation. Randomization was done with a minimization technique. The primary endpoint was event-free survival (EFS). Analysis were done by intention to treat.

Results

Between August 1995 and October 2003, 325 patients between 15 to 72 years of age were randomized to receive either DXM (163 patients) or PDN (162 patients). After induction and first consolidation course, 131 (80,4%) patients in DXM group and 124(76,5%) in PDN group achieved CR. No significant difference was observed between the 2 treatment groups regarding EFS: P=0.82, hazard ratio 0.97, 95% confidence interval 0.75-1.25, the 6-year EFS rates (±SE) were 25.9%(3.6%) vs. 28.7% (3.5%). Disease-Free survival (DFS) from CR was similar in DXM and PDN group: hazard ratio1.03, 95% confindence interval 0.76-1.40. The 6-year DFS rate was 32.3% (DXM) vs. 37,5% (PDN) group, the 6-year cummulative incidence of relapse was 32.3 (DXM) vs. 37.5% (PDN) group, the 6-year cumulative incidence of relapse was 49.8% vs. 53.5% (Gray test: P=0.30) and of death was 18% vs. 9% (Gray test: P=0.07).

Conclusions

In the ALL-4 trial in adult patients, DXM did not show any advantage compared to PDN. This study is registered with Clinical Trials gov. number NCT00002700.

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years of age or less with a sibling donor were assigned to undergo an allogeneic hematopoietic stem cell transplantation (allo-SCT), while patients without the sibling donor who were 20 to 60 years of age were randomized to receive either arm A autologous stem cell transplantation (auto-SCT) followed by low dose maintenance chemotherapy or arm B high dose maintenance chemotherapy with prophylactic CNS irradiation. Both maintenances contained vincristine, adriamycine and either DXM (VAD) or PDN (VAP). Patients were eligible for the second randomization if the following criteria were fulfilled: CR was achieved after induction and/or consolidation treatment, allo-SCT was not planned (see below), absence of very high features (mature B cell phenotype, acute undifferentiated leukemia or Philadelphia chromosome positive ALL) absence of severe cardiac, pulmonary, neurological and metabolic disease, adequate liver (bilirubin < 2mg/dl) and renal (creatinine <2 mg/dl) function tests, a suitable bone marrow function in terms of CFU-GM *in vitro* growth (more than 2 x 10^4 cells/kg) -and cellularity (nucleated cells more than 2 x 10^8/ kg), with HIV negativity after completion of MA consolidation, and signed informed consent.

Patients between 15 and 19 years of age, without a donor (see below) were eligible for the 2nd randomization if at least one of the following were present: initial WBC > 30 x 10^9/l, initial CNS or other extramedullary localization, or if CR was achieved after > day 28. The remaining younger patients without high risk features or patient older than 60 years had to receive Arm B. Patients <50 years old with a HLA-matched (geno and phenotypic) family donor or with existence of family donor missmatched for one HLA locus (A, B, or DR) or with a matched unrelated donor (optional), together with all the conditions mentionned for the second randomization were eligible for allo-SCT. The schedule and dose of cytotoxic drugs and chemotherapy courses are presented in Table 1.

The recommended conditioning regimen for allo- and auto-SCT was cyclophosphamide (60 mg/kg on two consecutive days) and total body irradiation fractionated over three days, for a total dose of 1200 cGy. The graft versus host disease (GvHD) prophylaxis in most centers was cyclosporine and short course of methotrexate (13). T-cell depletion of the allogeneic graft was performed in 13 cases by elutriation or by alemtuzumab “in the bag” (14).

Complete remission was defined as a morphologically normal marrow with less than 5% of blasts and normal peripheral blood and differential counts. Partial remission was defined as a treatment response with reduction of leukemic marrow blasts for more than 50% of blasts at diagnosis, and/or hypoplastic marrow and/or cytopenia of peripheral blood count. Refractory patients were defined as patients who did not reach CR after induction and first intensive consolidation. Among patients who reached CR, relapse was defined as >5% blasts in bone marrow. A diagnosis of

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extramedullary relapse was based on tissue diagnosis in case of clinical symptoms or organ or tissue infiltration and cerebrospinal fluid cytology in case of meningeal relapse. Risk factors were defined according to Gökbuget et al.(15).

Statistical analysis

The ALL-4 trial was a 2x2 factorial design phase III study evaluating efficacy and toxicity of DXM vs. PDN and of auto-SCT followed by low dose maintenance vs. prophylactic CNS irradiation with high dose maintenance. The primary endpoint for the comparison DXM vs. PDN was event-free survival (EFS). EFS was calculated from the date of CR until the date of first relapse or of death in first CR; patients who did not reach CR after induction will be considered as events at time 0. By definition all patients who died in CR were considered as cases of treatment-related mortality (TRM). The duration of survival was calculated from the date of randomization until the date of death; patients still alive were censored at their last follow-up. For the comparison of second randomization (auto-SCT and low dose maintenance vs. prophylactic CNS irradiation and high dose maintenance) the starting point was the date of randomization. This study was powered to detect a 15% treatment difference in the 3-year EFS rates (45% in DXM group), corresponding to hazard ratio (HR) of 0.66. A minimum of 308 patients had to be randomized, of whom 192 had to be followed until an event (2-sided alpha=5%, beta=20%).

Actuarial curves were calculated according to the Kaplan-Meier technique (16). The standard errors (SE) of the estimates were computed using the Greenwood formula (16). The estimates of the incidence of relapse and of death in CR, and their corresponding standard errors, were obtained using the cumulative incidence method, in which the risks of death in CR and of relapse were considered as competing risks (16). The statistical significance of differences between actuarial curves was tested using the two-tailed log-rank test (16), whereas the Gray test was used for the cumulative incidences (17). A Cox proportional hazards model was used to obtain the estimate and the 95% confidence interval (CI) of the hazard ratio (HR) of the instantaneous event rate in one group compared with in another group, as specified by a given variable, and the Wald test was used to determine the prognostic significance (16). This model was also used to determine the relative prognostic importance of several factors. The database was frozen in August 2007. SAS 9.1 statistical software (SAS Institute Inc, Cary, NC, USA) was used.

Results

Patient's characteristic according to the 1st randomization

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Between August 1995 and October 2003, 325 patients between 15 to 72 years of age with ALL or LBL were registered in ALL-4 study and randomized to receive either DXM or PDN. Patient characteristics according to the treatment arm are presented in Table 2.

Distribution of age and sex were similar in both groups; 94% of patients had ALL. The initial of CNS infiltration was found in 72 patients and its incidence (22%) was similar in the two treatment groups. B-lineage ALL was documented in 65% of the patients by immunophenotyping. The majority of the patients (70%) fulfilled the criteria for high risk ALL. In 215 (66%) patients cytogenetic analysis was successfully done. Among these patients, in 54 (25%) cytogenetic analysis was normal, while in 23% of them Ph positive ALL was documented. The median follow up was 6.6 years with a range from 0.5 to 11.7 years.

A total of 77 (23%) patients have been allografted in CR1 and 78 (24%) have been randomized for the 2nd question. The impact of the 1st randomization group DXM vs. PDN on the last step of treatment was quite minor. Failure, relapse and toxicity were the main reason of stopping therapy and 30% of patients finished therapy according to the protocol.

Treatment outcome

Table 3. summarizes the treatment outcome according to the 1st randomization. The similar CR rate was achieved for both groups. A total of 131 (80.4%) patients in DXM group and 124 (76.5%) patients in PDN group achieved CR rate after induction and first consolidation course.

There was no difference between DXM vs. PDN with respect to primary resistance, hypoplasia and early death. The remission rate for patients with CNS infiltration was practically identical for both groups, 6 out of 8 patients in DXM group vs. 6 out of 9 patients in PDN group.

Among patients who reached CR, the relapse rate was also similar for both groups: 48.9% for DXM group vs. 52.4% for PDN group. No significant difference was observed between the 2 treatment groups regarding EFS P=0.82, hazard ratio 0.97, 95% confidence interval 0.75-1.25, the 6-year EFS rates were 25.9% (DXM) vs. 28.7% (PDN) (Fig.2A).

No significant difference was observed between the 2 treatment groups regarding overall survival either: P = 0.45, hazard ratio 1.11, 95% confidence interval 0.85-1.45, 6-year survival rates were 30.6% (DXM) vs. 35.2% (PDN) (Fig 2B).

As indicated in Figure 2C, DFS was similar in DXM group vs PDN group: P=0.83, hazard ratio 1.03, 95% confidence interval 0.76-1.40. The 6-year DFS rates from CR were 32.3% (DXM) vs

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37.5% (PDN) group. The 6-year cumulative incidence (±SE) of relapse was 49.8% (±4.5%) vs 53.5% (±4.6%) (Gray test: P=0.30), whereas the 6-year cumulative incidence (±SE) of death was 18.0% (±3.4%) vs 9.0% (±2.6%) (Gray test: P=0.07).

A trend for shorter overall survival from CR was found for DXM compared to PDN group: P=0.18, hazard ratio 1.24, 95% confidence interval 0.90-1.70, the 6-year rates were 35.2% vs. 43.7% (Fig. 2D.). Using the Cox model, the trend in disfavor of DXM persisted: the comparison DXM vs PDN adjusted for the initial WBC and age yield P=0.11, hazard ratio 1.30, 95% confidence interval 0.94-1.79.

Toxicity

Grade III-IV toxicities according to the randomized steroid group, observed during induction therapy and consolidation are given in Table 4.

The incidence of severe toxicities was similar for DXM group and PDN group. A trend for higher incidence of hyperglycemia was documented in DXM group. In both treatment arms leukemia was the main cause of death (data not shown). In patients who reached CR, 18% (DXM group) vs 10.5% (PDN group) died without relapse. Most of the mortality was related to allo-SCT. The predominant causes of death following allografting were infections, severe GvHD and organ toxicity.

Discussion

DXM given as a steroid therapy for adult ALL/LBL in the ALL-4 trial of the EORTC-Leukemia Group did not show any benefit in the treatment outcome compared to PDN. Antileukemic efficacy did not seem to differ between the DXM and PDN group. Thus, the results of ALL-4 study did not support the experience from several pediatric studies using historical controls and of 2 large prospectively randomized clinical trials (18, 19), showing that patients receiving DXM have a better outcome. Data reporting that DXM penetrates better in the CNS and has enhanced activity against disease (9-11) could not be confirmed in ALL-4 trial.

Reasons for non superiority of DXM in our trial might be the type of patient treated (adult versus children) and the dosages of DXM and PDN. The Children's Cancer Group trial CCG-1922 (18) evaluated the role of DXM compared to PDN in standard risk ALL during induction, consolidation and maintenance therapy (< 10 years of age and WBC counts $<50x10^9$/L). In a daily dose of 6 mg/m^2 for 28 days they administered to the patients randomized in the DXM arm

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168 mg/m^2 in the induction phase, 120 mg/m^2 during the consolidation, 210 mg/m^2 during the delayed intensification (NOTE: also on the PDN arm) and 150 mg/m^2 during the maintenance phase. The daily dose of PDN in induction was 40 mg/m^2 and the expected total dosages given were, respectively, 1160 mg/m^2, 800 mg/m^2, and 600 mg/m^2 per maintenance cycle. They found a significant difference in event-free survival at 6 years (85% vs. 77%), but no difference in overall survival. Furthermore there was a significant difference in isolated CNS relapse rate and a trend to a difference in bone marrow relapse rate in favor of the DXM arm. Patients using DXM developed more often myopathy and hyperglycemia. No difference was found in infection frequency and severity between both arms.

In the ALL 97/99 trial of the MRC Childhood Leukemia Working Party (19) standard and high risk ALL patients (very high risk excluded) were randomized to receive either PDN or DXM. They had to receive a DXM daily dose of 6.5 mg/m^2 for 28 days, corresponding to a total dose 182 mg/m^2 in induction, 130 mg/m^2 as interim maintenance, 140 mg/m^2 during delayed intensification (NOTE: also in the PRED arm) and 97.5 mg/m^2 each 12 weeks cycle as continuation therapy. In the PDN-arm, the daily dose of PDN was 40 mg/m^2 and the total dosages were 1160 mg/m^2, 400 mg/m^2 and 600 mg/m^2 per maintenance cycle, respectively. They also found at 5 years a significant difference in event-free survival in favor of DXM arm (84% vs. 76%), but not in terms of overall survival. The CNS risk of relapse was significantly decreased but not the bone marrow relapse. There was a significant excess of overall toxicity in the DXM group due to behavioral problems, myopathy and severe osteopenia, as well as a decreased quality of life (20) but not due to infections.

The ALL-4 trial included only patients over the age of 18 years. Majority of patients were high risk ALL/LBL. A total dose of 112 mg/m^2 DXM during induction and 320 mg total dose (corresponds with 160 – 200 mg/m^2) during the maintenance phase was administered. The PDN dosages were 840 mg/m^2 and 800 mg total dose (approx. 400-450 mg/m^2). We found neither differences in disease-free and overall survival, nor in relapse incidence and pattern, while a trend for higher toxicity was observed in the DXM arm.

The adult patients in our trial received only 65-70% of the DXM dose reported in the childhood ALL trials (18, 19) but they also received a lower total dose of PDN (approx. 70%) than the children. In addition, the type of patients treated differs largely from that of the pediatric trials with respect to age and to the percentage of high risk patients. The difference of DXM efficacy in children and adult ALL could be also related to a different biology of the disease in children and adults (21), and different intensity of treatment protocols used (22). More aggressive

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chemotherapy together with better prognosis of ALL in children (23, 24), could be of importance in predicting better response to steroids.

From a pilot trial (06/99) of the German Multicenter Study Group for Adult ALL (GMALL) (25) evaluating the efficacy of different dosages of DXM, the authors reported that the "low" dose induction schedules of DXM (90 or 120 mg/m^2 total dose) showed a similarly good antileukemic efficacy (CR rate of ~80%) as their higher dose schedule (260 mg/m^2) whereas the incidence of early deaths and severe infections was significantly lower in patients receiving the low total dose schedule. Although this is not a randomized trial, this study has already led to a preference for DXM instead of PDN in Germany. In the ALL-4 study the patients received 112 mg/m^2 total dose of DXM during induction, which is similar to the "low" dose group in the GMALL study. The CR rate is similar (78%) but the incidence of serious infections and early deaths is higher compare to the data of the "low "dose schedule of DXM in the GMALL pilot study.

Serious toxicity in adults could strongly influence the outcome and thus change the results of steroid therapy. Some data clearly showed that treatment related toxicity is significantly higher in older patients (26). In addition it seems that intensive DXM therapy is more immunosuppressive and hence more frequently associated with serious infections than PDN in ALL trials (12, 27, 28). On the other hand steroid toxicity in adult could not be compared to the steroid toxicity in children because of the different postremission treatment strategy. The majority of adult patients who are eligible for allo-SCT underwent allotransplant in 1st CR. Most of the children in 1st CR received intensified chemotherapy courses and maintenance chemotherapy which are quite tolerable in this age group of patients. Contrary to that, Allo-SCT performed with standard conditioning is still associated with high mortality rate ranging from 15% to 30% (29, 30). Recently it was shown that polymorphism of genes involved in corticosteroid response is important predictor of it's toxicity. Glutathione-S-transferase-M1 genotype might influence the severity of infection in childhood ALL (31)

In conclusion DXM as a steroid therapy for adult patients with ALL/LBL at the dose given in the ALL-4 trial did not show any advantage compared to PDN. The toxicity of both drugs during induction therapy and consolidation was similar.

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BL provided the patient care and wrote the manuscript; SS revised the statistical analysis and wrote the results od manuscript; RW provided the patient care and contribute in writing the manuscript; PM, JPM, GF, ZB, BJ, WF, DB, HS, MM, GV, RDB, DN provided the patient care and commented on the manuscript, CG collected clinical data, SA and TDW provided patient care and commented on the manuscript.

The authors reported no potential conflicts of interest.

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References

1. Gaynon PS, Lustig RH. The use of glucocorticoids in acute lymphoblastic leukemia of childhood: molecular, cellular, and clinical considerations. J Pediatr Hematol Oncol 1995;17:1-12.
2. Smith M, Arthur D, Camitta B Carroll AJ, Crist W, Gaynon P, Gelber R, Heerema N, Korn EL, Link M, Murphy S, Pui CH, Pullen J, Reamon G, Sallan SE, Sather H, Shuster J, Simon R, Trigg M, Tubergen D, Uckun F, Ungerleider R. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. J Clin Oncol. 1996;14:18-24.
3. Visser JH; Wessels G; Hesseling PB; Louw I; Oberholster E; Mansvelt EP Prognostic value of day 14 blast percentage and the absolute blast index in bone marrow of children with acute lymphoblastic leukemia. Pediatr Hematol Oncol 2001 Apr-May;18(3):187-91.
4. Gokbuget N, Hoelzer D. Recent approaches in acute lymphoblastic leukemia in adults. Rev Clin Exp Hematol. 2002;6:114-41.
5. Pui CH, Ewans WE. Treatment of acute lymphoblastic leukaemia. N Engl J Med. 2006; 354:166-178.
6. Cantrill HL, Waltman SR, Palberg PF, Zink HA, Becker B. In vitro determination of relative corticosteroid potency. J Clin Endocrinol Metab 1975; 40:1073-1077.
7. Kaspers GJ, Veerman AJ, Popp-Snijders C, Lomecky M, Van-Zantwijk CH, Swinkels LM, Van-Werin ER. Comparison of the antileukemic activity in vitro of dexamethasone and prednisolone in childhood acute lymphoblastic leukaemia. Med Ped Oncol; 1996 27:114-121.
8. Balis FM, Lester CM, Chrousos GP, Heideman RI, Poplak DG. Differences in cerebrospinal fluid penetration of corticosteroids: possible relationship to the prevention of meningeal leukaemia. J Clin Oncol; 1987 5:202-207.
9. Jones B, Freeman AL, Shuster JJ, Jacquillat C, Weil M, Pochedly C, Sinks L, Chevalier L, Maurer HM, Koch K. Lower incidence of meningeal leukaemia when prednisolone is replaced by dexamethasone in the treatment of acute lymphoblastic leukaemia. Med Ped Oncol, 1991: 19:269-275.
10. Veerman AJ, Hahlen K, Kamps WA, Van Leeuwen EF, De Vaan GA, Solbu G, Suciu S, Van Wering ER, Van der Does-Van der Berg A. High cure rate with a moderately intensive treatment regimen in non-high-risk childhood acute lymphoblastic leukemia: results of protocol ALL VI from Dutch Childhood Leukemia Study Group. J Clin Oncol. 1996;14:911-918.

DOI: 10.3324/haematol.2009.018580

11. Siverman LB, Gelber RD, Dalton VK, Young ML, Sallan SE. Improved outcome for children with acute lymphoblastic leukemia: results of the Dana-Farber Consortium Protocol 91-01. Blood 2001; 97:1211-1218.
12. Hurwitz C, Silverman LB, Schorin MA, Clavell LA, Dalrton VK, Glick KM, Gelber RD, Sallan SE. Substituting dexamethasone for prednisone complicates remission induction in children with acute lymphoblastic leukaemia. Cancer 2000; 88:1964-1969.
13. Storb R, Deeg HJ, Whitehead J, Appelbaum F, Beatty P, Bensinger W, Buckner CD, Clift R, Doney K, Farewell V, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft-versus-host disease after marrow transplantation for leukemia. N Engl J Med 1986;314:729-35
14. De Witte T, Awwad B, Boezeman J, Schattenberg A, Muus P, Raemaekers J, Preijers F, Strijckmans P, Haanen C. Role of allogenic bone marrow transplantation in adolescent or adult patients with acute lymphoblastic leukaemia or lymphoblastic lymphoma in first remission. Bone Marrow Transplant 1994; 14:767-74.
15. Gökbuget N, Hoelzer D, Arnold R, Bohme A, Bartram CR, Freund M, Ganser A, Kneba M, Langer W, Lipp T, Ludwig WD, Maschmeyer G, Rieder H, Thiel E, Weiss A, Messerer D. Treatment of adult ALL according to the protocols of the German Multicenter Study Group for Adult ALL (GMALL). Hemat/Oncol Clin North Am 2000; 14:1307-25.
16. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. Statistics for Biology and Health. Springer-Verlag, New-York. 1997.
17. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141-54.
18. Bostrom BC, Sensel MR, Sather HN, Gaynon PS, La MK, Johnston K, Erdmann GR, Gold S, Heerema NA, Hutchinson RJ, Provisor Aj, Trigg ME. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from Children Cancer Group. Blood. 2003; 101:3809-3817.
19. Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, Eden TOB, on behalf of the Medical Research Council Childhood Leukemia Working Group. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. Brit J Haematol. 2005; 129:734-745.

DOI: 10.3324/haematol.2009.018580

20. de Vries MA, van Litsenburg RR, Huisman J, Grootenhuis MA, Versluys AB, Kaspers GJ, Gemke RJ. Effect of dexamethasone on quality of life in children with acute lymphoblastic lekaemia: a prospective observational study. Health Qual Life Outcomes. 2008; 6:103-07
21. Pui CH, Campana D. Age-related differences in leukemia biology and prognosis: the paradigm of MLL-AF4-positive acute lymphoblastic leukemia. Leukemia. 2007; 21:593-4.
22. Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, Richards SM, Lazarus HM, Franklin IM, Litzow MR, Ciobanu N, Prentice HG, Durrant J, Tallman MS, Goldstone AH. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood. 2005; 106:3760-7.
23. Schrappe M, Camitta B, Pui CH, Eden T, Gaynon P, Gustafsson G, Janka-Schaub GE, Kamps W, Masera G, Sallan S, Tsuchida M, Vilmer E. Long term results of large prospective trials in childhood acute lymphoblastic leukemia. Leukaemia. 2000; 14:2193-2194.
24. Hann I, Vora A, Richards S, Hill F, Gibson B, Lilleyman J, Kinsey S, Mitchell C, Eden OB. Benefit of intensified treatment for all children with acute lymphoblastic leukaemia: results from MRC UKALL XI and MRC ALL97 randomised trials. UK Medical Research Council's Working Party on Childhood Leukaemia. Leukemia 2000; 14:356-63.
25. Goekbuget N, Bauer KH, Beck J, Diedrich H, Lamprecht M, Leimer L, Lipp T, Neteler J, Reutzel R, Rutjes J, Schmid M, Staib P, Stelljes M, Hoelzer D. Dexamethasone Dose and Schedule Significantly Influences Remission Rate and Toxicity of Induction Therapy in Adult Acute Lymphoblastic Leukemia (ALL): Results of the GMALL Pilot trial 06/99. Blood 2005; 106:1832 (abstr)
26. Kantarjian H, Thomas D, O'Brien S, Cortes J, Giles F, Jeha S, Bueso-Ramos CE, Pierce S, Shan J, Koller C, Beran M, Keating M, Freireich EJ. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 2004; 101:2788-801.
27. Ito C, Evans WE, McNinch L, Coustan-Smith E, Mahmoud H, Pui CH, Campana D. Comparative cytotoxicity of dexamethasone and prednisolone in childhood acute lymphoblastic leukemia. J Clin Oncol 1996; 14:2370-2376.

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28. Belgaumi AF, Al-Bakrah M, Al-Mahr M, Al-Jefri A, Al-Musa AR, Saleh M, Salim MF, Osman M, Osman I, El-Solh H. Dexamethasone-associated toxicity during induction therapy for childhood acute lymphoblastic leukemia is augmented by concurrent use of daunomycin. Cancer 2003; 97:2898-2903.
29. Labar B, Suciu S, Zittoun R, Muus P, Marie JP, Peetermans M, Strijckmans P, Willemze R, Feremans W, Jaksic B, Bourhis JH, Burghouts JP, de Witte Th. Allogeneic stem cell transplantation in acute lymphoblastic leukemia for leukemia for patients < 50 years in first complete remission: results of the EORTC ALL-3 trial. Haematologica 2004; 89: 809-817
30. Willemze R and Labar B. Postremission treatment for adult patients with acute lymphoblastic leukemia in first remission: is there a role for autologous stem cell transplantation? Semin Hematol. 2007; 44:267-73.
31. Marino S, Verzegnassi F, Tamaro P, Stocco G, Bartoli F, Decorti G, Rabusin M. Response to glucocorticoids and toxicity in childhood acute lymphoblastic leukemia: role of polymorphisms of genes involved in glucocorticoid response. Pediatr Blood Cancer. 2009; 53:984-91

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Table 1. Scheme of the ALL-4 Protocol.

Months	Registration	
1	**R1** **DXM 8 mg/m^2 i.v. or p.o. days 1-8, 15-22;** **PDN 60 mg/m^2 i.v. or p.o. days 1-8, 15-22;** Daunorubicine 30 mg/m^2 i.v. days 1,2,3, 15,16: Cyclophosphamide 750 mg/m^2 i.v. days 1,8; Vincristine 2 mg i.v. days 1,8,15,23; Methotrexate (MTX) 15 mg i.t. 1,8,15,22,28;	
2	**Consolidation Therapy „HAM“** High-dose cytarabine 1 g/m^2 i.v. as 2 hours infusion every 12 hours for 6 days Mitoxantrone 10 mg/m^2 i.v. for 3 days	
3	**Consolidation Therapy „MA“** MTX 1500 mg/m^2 i.v. in 30 minutes days 65,80 and folinic acid rescue Asparaginase (E. coli) 10.000 IU/m^2 in i hour infusion or i.m. days 66,81	
	R2 → **Arm A Auto-SCT**; **Allo-SCT** → **Arm B**	
	Arm A **Auto-SCT**	**Arm B** **CC –** Cyclophosphamide 1 g/m^2 i.v. day 1 Cytarabine 500 mg/m^2 in 24-hour infusion, day 1 6-MP 60 mg/m^2/day orally + MTX 15 mg/m^2/week orally starting 1 week after CC and stopping one week before the next course
	MTX i.t.	CNS irradiation 18 Gy MTX i.t.* first day of irradiation
		MA - Methotrexate 1500 mg/m^2 i.v. on day 1 Asparaginase 10.000 IU/m^2 i.v. or i.m.
		CC
	VAD** or VAP** + MTX i.t.*	**VAD/VAP** Vincristine 0,4 mg/day i.v. days 1-4 Adriamycin 12 mg/m^2/day i.v., days 1-4 DXM 40 mg/day days 1-4 or PDN 100 mg/day, days 1-4 MTX i.t.* day 1
	VAD or VAP + MTX i.t.	VAD or VAP + MTX i.t.
	6-MP + MTX***	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	stop treatment
	stop treatment	

* MTX i.t. = methotrexate i.t. (same dose as in induction therapy)

** VAD/VAP same dose as in arm B

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Table 2. Patient's characteristics according to the 1st randomization.

	Dexamethazone n=163 (100%)	Prednisolone n=162 (100%)
Sex (n, %)		
Male	90 (55)	97 (60)
Female	73 (45)	65 (40)
Age* (years)		
Median (range)	32 (15–68)	33.5 (15–72)
15 to <20 (n, %)	30 (18)	30 (19)
20 to <35 (n, %)	57 (35)	55 (34)
35 to <61 (n, %)	68 (42)	69 (43)
≥ 61 (n, %)	8 (5)	8 (5)
Disease* (n, %)		
ALL	153 (94)	152 (94)
NHL	10 (6)	10 (6)
WBC* (x 10^9/l)		
Median (range)	11.4 (0.8 - 373)	13.6 (0.9 - 934)
< 30 (n, %)	109 (67)	107 (66)
30 to <= 100 (n, %)	31 (19)	32 (20)
> 100 (n, %)	23 (14)	23 (14)
Immunophenotype (n, %)		
B-lineage (n, %)	106 (65)	111 (69)
T-lineage (n, %)	50 (31)	40 (25)
Biphenotypic (n, %)	5 (3)	4 (2)
AUL (n, %)	2 (1)	6 (4)
Unknown (n, %)	0 (0)	1 (1)
Cytogenetics (n, %)		
Failure (n, %)	19 (12)	15 (9)
NN (n, %)	27 (17)	28 (17)
Good risk (n, %)*	31 (19)	23 (14)
Presence of t(4;11) (n, %)	2 (1)	5 (3)
Presence of t(9;22)** (n, %)	29 (18)	28 (17)
Other bad risk (n, %)	18 (11)	13 (8)
Other abnormalities (n, %)	6 (4)	5 (3)
Unknown (n, %)	35 (22)	41 (25)
Extramedulary involvement (n, %)		
No (n, %)	117 (72)	115 (71)
CNS (n, %)	37 (23)	35 (22)
Other involvement (n, %)	9 (6)	12 (7)

* Good risk: hyperdiploidy, presence of 9p-, t(10;14)

** and/or presence of BCR/ABL, detected by RT-PCR

*** Other bad risk cytogenetics: hypodiploidy (<30), presence of t(8;14), complex abnormalities (>= 5 chromosomal abnormalities, excluding those patients with established translocations)

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Table 3. Treatment outcome for all patients and for patients randomized to receive DXM or PDN.

Variable	Dexamethazone n=163 (%)	Prednisolone n= 162 (%)
Overall response		
CR	131 (80.4)	124 (76.5)
PR	5 (3.1)	11 (6.8)
Resistance	6 (3.7)	7 (4.3)
Hypoplasia	5 (3.1)	4 (2.5)
Early Death	14 (9.8)	13 (8.0)
Not valuable	2 (1.2)	3 (1.9)
DFS status		
CCR	43 [32.8]	46 [37.1]
Relapse	64 [48.9]	65 [52.4]
BM only	44 [33.6]	48 [38.7]
CNS relapse only	3 [2.3]	5 [4.0]
CNS+BM	6 [4.6]	5 [4.0]
others	11 [8.4]	7 [5.8]
TRM**	24 [18.3]	13 [10.5]
Infection	11	7
Hemorrhages	1	3
GvHD	5	1
Other	7	2
Survival status		
Alive	50 (30.7)	58 (35.8)
Dead	113 (69.3)	104 (64.2)
Leukemia	51 (31.3)	56 (34.6)
Toxicity	43 (26.4)	31 (19.1)
Both	8 (4.9)	7 (4.3)
Other	11 (6.7)	10 (6.2)

* CNS_{CR} – CR for patients with CNS infiltration at diagnosis
**: after AlloSCT: 14 (2 in Ph+ pts) vs 9 (1 in Ph+)

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Table 4. Toxicity grade III-IV according to 1st randomization (DXM vs. PDN) and treatment phase.

Induction course		
Variable	DXM N=114 (100%)	PDN N=112 (100%)
Hemorrhages	6 (5.2)	8 (7.2)
Presence of hyperglycemia	19 (16.7)	12 (10.7)
Insomnia*** / neurotoxicity	5 (4.4)	4 (3.6)
Infection	62 (54.4)	67 (59.8)
Others*	41 (36.0)	39 (34.8)
Consolidation course		
Variable	DXM N=68 (100%)	PDN N=61 (100%)
Hemorrhages	3 (4.4)	8 (7.2)
Presence of hyperglycemia	NA**	NA**
Insomnia*** / neurotoxicity	4 (5.9)	3 (6.5)
Infection	57 (83.8)	48 (78.8)
Others*	31 (45.6)	24 (39.3)

* Other clinical relevant complications: nephrotoxicity, cardiotoxicity etc.
** NA – not applicable (information not collected)
***: recorded only during induction

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Figure 1. EORTC ALL-4 protocol: study design.

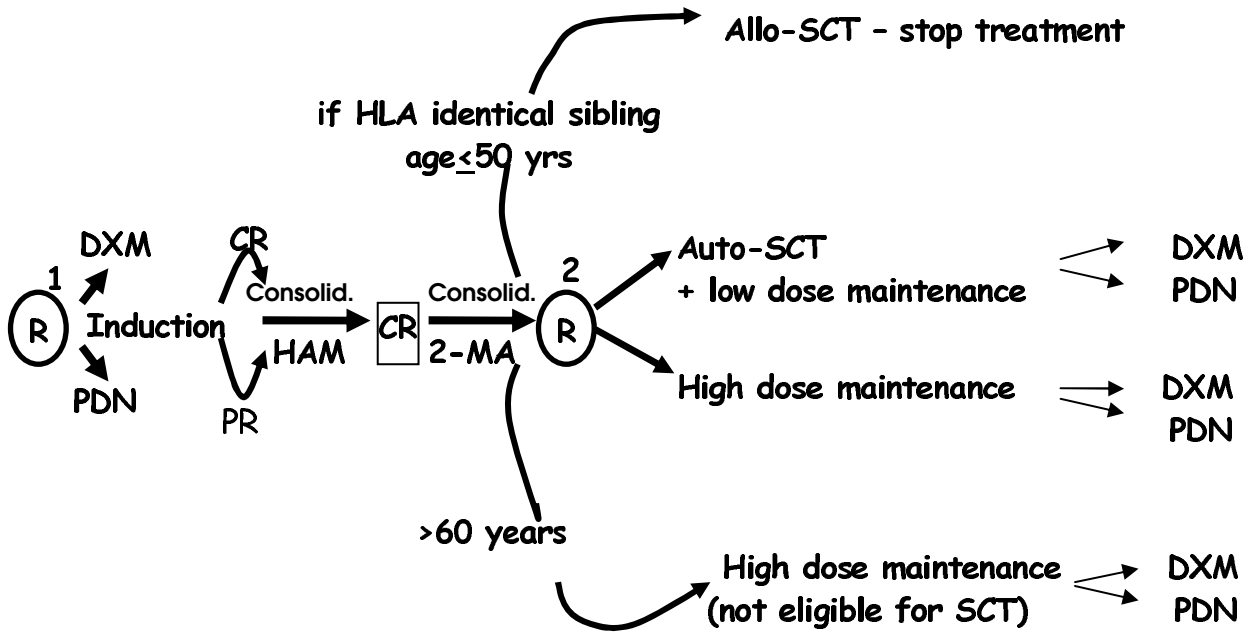

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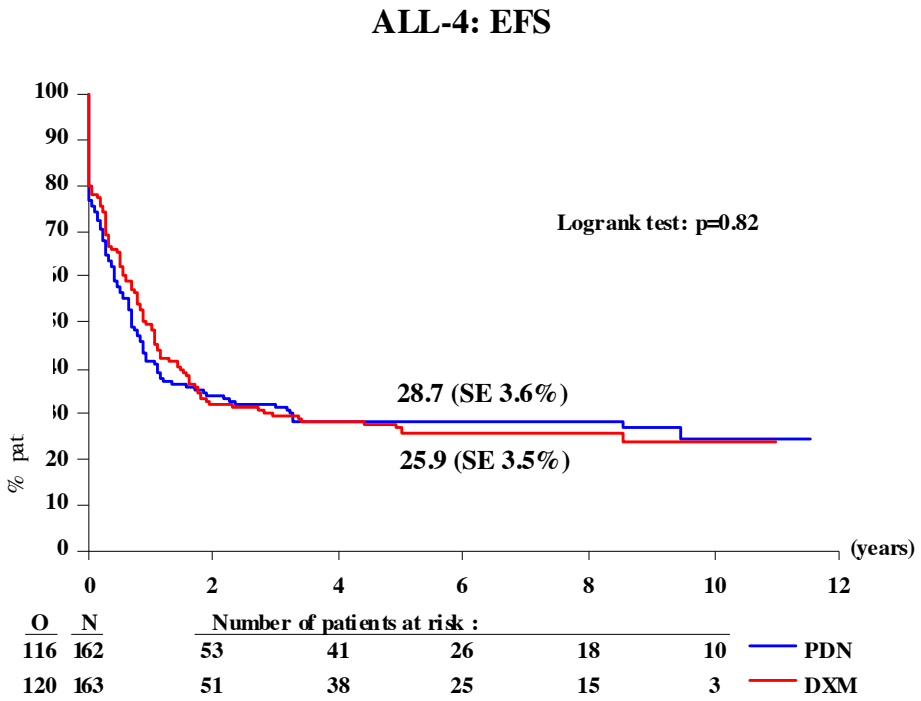
Figure 2. The 6-year of EFS (A) and overall survival (B) , DFS from CR (C) and survival from CR (D) according to the randomization DXM vs. PDN N = total number of patients; O = observed number of events; SE: Standard error (%).

A.



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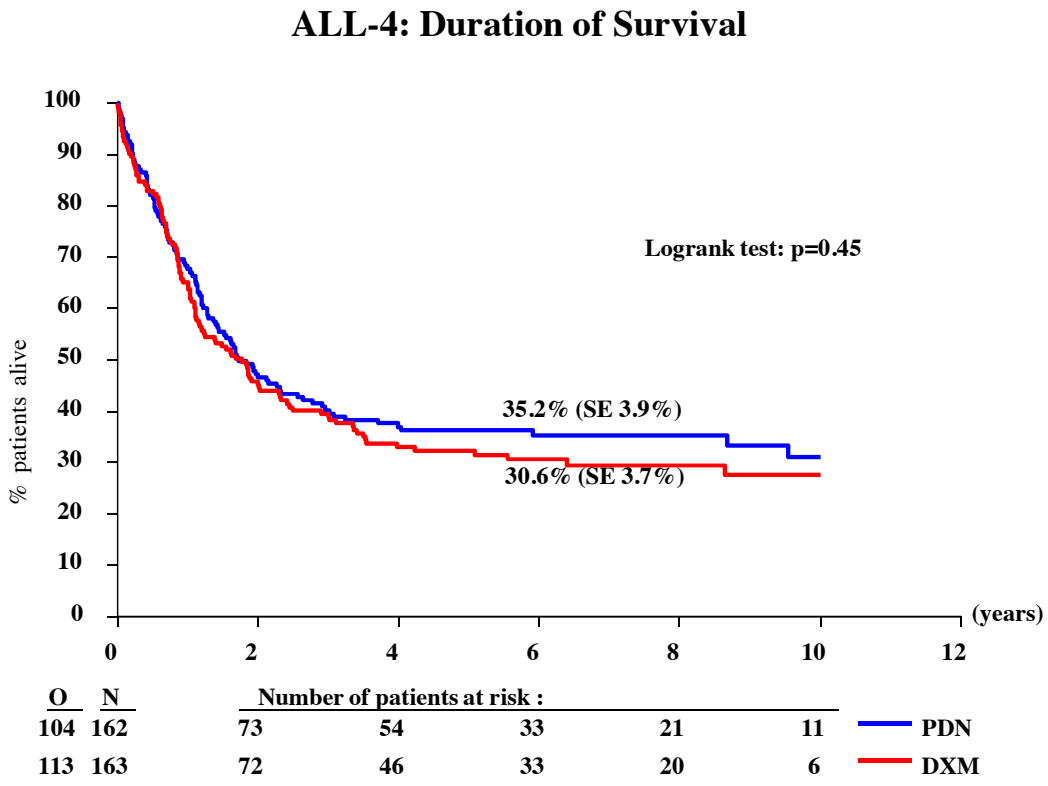
B.



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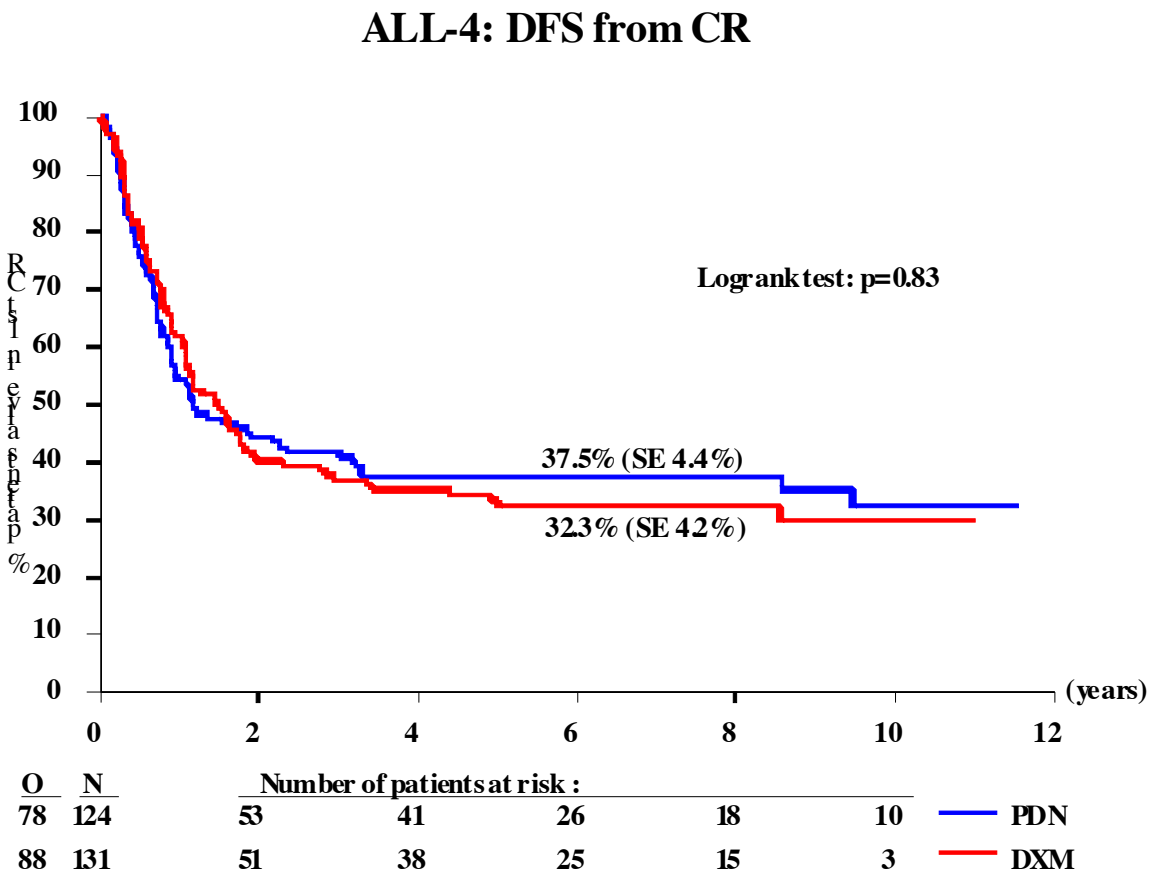
C.



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2D.