blood

Prepublished online September 8, 2005;
doi:10.1182/blood-2005-06-2305

XPD Lys751gln polymorphism: Etiology and outcome of childhood acute myeloid leukemia. A children's oncology group report

Parinda A Mehta, Todd A Alonzo, Robert B Gerbing, James S Elliott, Tiffany A Wilke, Rebekah J Kennedy, Julie A Ross, John P Perentesis, Beverly J Lange and Stella M Davies

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.

Blood First Edition Paper, prepublished online September 8, 2005; DOI 10.1182/blood-2005-06-2305

XPD Lys751Gln Polymorphism: Etiology and Outcome of Childhood Acute Myeloid Leukemia. A Children's Oncology Group report.

Parinda A Mehta[1], Todd A Alonzo[2], Robert B Gerbing[3], James S Elliott[1], Tiffany A Wilke[1], Rebekah J Kennedy[1], Julie A Ross[4], John P Perentesis[1], Beverly J Lange[5] and Stella M Davies[1]

[1] Division of Hematology/Oncology, Department of Pediatrics, University of Cincinnati College of Medicine, and Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, [2]University of Southern California Keck School of Medicine, [3]Children's Oncology Group, Arcadia, California, [4]Department of Pediatrics, University of Minnesota Cancer Center, [5]Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia

Correspondance : Parinda A Mehta, M.D.

MLC 7015

Cincinnati Children's Hospital and Medical Center

3333 Burnet Ave,

Cincinnati, OH 45229

Abstract

Genetic polymorphisms result in inter-individual variation in DNA repair capacity, and may in part, account for susceptibility of a cell to genotoxic agents, and to malignancy. Polymorphisms in XPD, a member of the nucleotide excision repair pathway, have been associated with development of treatment-related AML and with poor outcome of AML in elderly patients. We hypothesized that XPD Lys751Gln polymorphism may play a role in causation of AML in children and, as shown in adults, may affect the outcome of childhood AML therapy. 456 children treated for de novo AML were genotyped at XPD exon 23. Genotype frequencies in cases were compared with normal control frequencies and patient outcomes were analyzed according to genotype. Gene frequencies in AML patients and normal controls were similar. There were no significant differences in overall survival (p= 0.82), event-free survival (p=0.78), treatment-related mortality, (p=0.43) or relapse rate (RR) (p=0.92) between patients with XPD751AA vs. 751AC vs. 751CC genotypes, in contrast to reports in adult AML. These data, representing the only data in pediatric AML, suggest that XPD genotype does not affect the etiology or outcome of childhood AML.

Introduction

DNA is continuously damaged by endogenous and exogenous mutagens. Repair of DNA damage is a complex process carried out by an array of DNA repair pathways, including nucleotide excision and base excision repair pathways. The nucleotide excision repair (NER) pathway eliminates the widest variety of damage to the human genome, including UV-induced photoproducts, bulky monoadducts, cross-links and oxidative damage.[1]

Hereditary genetic defects in DNA repair lead to increased risk of cancer. Individuals with xeroderma pigmentosum (XP), a rare autosomal recessive disease resulting from a defect in NER of UV damaged DNA, have a 1000 fold increased risk of skin cancer.[2] Cell fusion analyses have identified seven genetic complementation groups (XPA to XPG) that encode for proteins participating in different steps of the NER pathway.[3,4] Xeroderma pigmentosum complementation group D (XPD) is a major participant in NER pathway and is also involved in transcription initiation, control of cell cycle and apoptosis.[5]

XPD functions as an evolutionarily conserved ATP-dependent helicase within the multi-subunit transcription repair factor complex, TFIIH.[6,7,8] TFIIH has two distinct roles, first in basal transcription carried out by RNA polymerase II and secondly in NER of DNA damage. It appears that XPD protein needs to be present to maintain the stability of the TFIIH complex. XPD possesses both single-strand DNA dependent ATPase and 5'-3' DNA helicase activities and is thought to participate in DNA unwinding during NER and

transcription.[9,10] Mutations in the XPD gene can completely prevent DNA opening and dual incision, steps that lead to the repair of DNA adducts.[11]

Genetic polymorphisms result in inter-individual variation in DNA repair capacity, and may in part account for differences in susceptibility of a cell to genotoxic agents, and to malignancy.[12,13] Several single nucleotide polymorphisms, including an adenine (A) to cytosine (C) (A→C) transition which leads to Lys751Gln in exon 23 of the XPD gene, have been shown to be associated with elevated frequency of chromosomal aberrations and a variety of environmentally induced cancers in adults.[14,15,16,17] There is also evidence that dysregulation of DNA repair proteins and NER pathways may be involved in pathogenesis and prognosis of some myeloid leukemia.

Recent data from elderly AML patients treated on MRC11 trial showed reduced EFS and OS along with increased risk of developing treatment related leukemia in XPD 751 glutamine homozygotes (CC), suggesting that the glutamine variant confers greater protection against chemotherapy-induced leukemic blast cell death, leading to earlier disease relapse and ultimately shorter overall survival.[18] In this study we show that, in contrast to the adult data, XPD751 does not influence outcome of therapy in children with AML.

Patients and Methods

Patients

The study population included 456 children with de novo AML treated on Children's Cancer Group (CCG) therapeutic studies CCG-2941(n=37) and CCG-2961(n=419) between 1995 and 2002. Clinical data, including age, sex, white blood cell (WBC) count at diagnosis, race, presence of chloroma, presence of CNS disease, and immunophenotype were collected prospectively (Table 1). Cases were classified on the basis of criteria established and revised by the French-American-British (FAB) Cooperative Study Group by central pathology review. All FAB categories except acute promyelocytic leukemia (APL – AML M3) were eligible for enrollment and were treated with the same chemotherapy regimens. These studies were approved by the Cincinnati Children's Hospital Medical Center's institutional review board. Informed consent was provided according to the Declaration of Helsinki.

578 normal blood donors were randomly selected and used to determine control genotype frequencies. Four hundred and thirty two were white and 146 were black controls.

Chemotherapy Treatment Regimen

CCG-2961 study was a randomized phase III trial of intensively timed induction, consolidation, and intensification therapy for pediatric patients with previously untreated AML or MDS.[19] The study was conducted between August 1996 and December 2002. CCG 2941 was a feasibility pilot of the same chemotherapy regimen that preceded the

randomized study. Induction included 5 drugs: idarubicin, etoposide, dexamethasone, cytarabine, and 6-thioguanine (IDA DCTER) given on days 0-3 followed by 5 drugs (daunorubicin, etoposide, dexamethasone, Ara-C and 6-thioguanine) (DCTER) given on days 10-13.[20] Upon recovery of white blood cell and platelet counts, patients were randomly assigned to consolidation therapy consisting of the same sequence of drugs or to fludarabine/ cytarabine /idarubicin. Intrathecal cytarabine was used for CNS prophylaxis. Patients with matched-related donors were assigned to allogeneic marrow transplant intensification. Pre-transplant cytoreduction was busulfan and cyclophosphamide. Patients without a related donor received high-dose cytarabine/L-asparaginase (Capizzi II), and additional intrathecal cytarabine. After recovery from chemotherapy, patients were randomized again to either receive Interleukin-2 or standard follow-up care. Transplanted patients were not eligible for randomization to interleukin-2.

XPD genotyping

DNA extracted from diagnostic marrow samples using standard methods was normalized to 10 ng/µl. Genotyping was performed using a fluorescence based allelic discrimination assay (TaqMan, Applied Biosystems, Foster City, CA). Gene-specific polymerase chain reaction (PCR) primers and fluorogenic probes for allelic discrimination are described in Table 2.

PCR cycling reactions were performed in 96-well micro titer plates in a GeneAmp PCR System 9600 (Perkin-Elmer). For each 25 µl reaction, 10 ng DNA template were added to the reaction mixture containing wild-type VIC and variant FAM probe, PCR mastermix (Applied biosystems, CA, USA) and forward and reverse primers (final concentration 0.3 µM). Thermocycling was performed with an initial 50°C incubation for 2 minutes followed by a 10-minute incubation at 95°C. A two-step cycling reaction was performed for 40 cycles with denaturation at 95°C for 15 seconds, and annealing and extension at 62°C for 1 minute. Results were analyzed by the automated TaqMan allelic discrimination assay using sequence detection system 2.1 software (ABI TaqMan 7700, Applied Biosystems).

DNA from normal controls was extracted using standard techniques and genotyped as described for cases. Genotyping results were duplicated in 10% of samples; concordance between repeats was 100%. Furthermore, 10% of the samples were also genotyped using direct sequencing; concordance with TaqMan genotyping was 100%.

Statistical Analysis

Data were analyzed from CCG-2941 and CCG-2961 through April 2005 for both studies. The significance of observed differences in proportions was tested using the Chi-squared test and Fisher's exact test when data were sparse. The Mann-Whitney test was used to determine the significance between differences in medians.[21] The Kaplan-Meier method was used to calculate estimates of overall survival (OS), event-free survival (EFS) and

disease-free survival (DFS).[22] Estimates are reported with their Greenwood standard errors.[23] Differences in these estimates were tested for significance using the log-rank statistic.[24] OS is defined as time from study entry to death from any cause. EFS is defined as time from study entry to failure at the end of two courses, relapse or death from any cause. DFS is defined as time from the end of one course of therapy to failure at the end of two courses, relapse or death from any cause. Cumulative incidence estimates were used to determine relapse rate (RR) and treatment-related mortality (TRM). RR is defined as time from the end of one course of therapy to failure at the end of two courses, relapse or death from progressive disease where deaths from non-progressive disease were competing events. TRM is defined as time from study entry to death from non-progressive disease where failures at the end of two courses, relapses and deaths from progressive disease were competing events. Differences between RR or TRM estimates were tested for significance using Gray's test.[25] Children lost to follow-up were censored at their date of last known contact or at a cutoff 6 months prior to April 2005. Cox regression was used for multivariate models that looked at differences between groups adjusting for study assignment, age, gender, race, and WBC count.

Results

Allele and genotype frequencies for cases and controls are shown in Table 3. XPD genotype frequencies for black and white controls were significantly different ($p<0.001$). Genotype frequencies did not differ by gender (data not shown). Comparison of genotype frequencies was therefore performed separately for white cases vs. white controls and black cases vs. black controls. Genotype frequencies were similar in white

cases and controls (Table 3; p=0.125) and black patients and black controls (p=0.239). The distribution of XPD genotypes was consistent with the Hardy–Weinberg equilibrium. Stratification of cases by age at diagnosis (0-2 yo vs. >2-10 yo vs. >10 yo), WBC count at diagnosis (<50,000 vs. ≥50,000), AML subtype, or cytogenetics revealed no difference in genotype frequencies. There were more XPD751AC patients compared to AA in hyperdiploid cases, however, this difference should be interpreted cautiously due to very small total number of patients with hyperdiploidy.

XPD genotype and Outcome

There were no significant differences in OS from study entry between patients with XPD751AA vs. 751AC vs. 751CC genotypes (53 ± 8% vs. 50 ± 8% vs. 45 ± 13% respectively at 5 years; log-rank p = 0.82; Figure 1). In addition, induction of remission did not vary by genotype (Table 1). When OS from end of one course of therapy for patients in remission was compared between different genotypes, there was no statistical difference between polymorphism subgroups; 57 ± 8% in XPD751AA vs. 58 ± 8% in AC vs. 52 ± 15% in CC patients at 5 years (log rank p=0.96).

Analysis of EFS from study entry in different genotypes also showed similar estimates. 41 ± 7% in XPD751AA vs. 38 ± 7% in AC vs. 41 ± 13% in CC patients at 5 years (log rank p=0.78) (Figure 2). Disease free survival (DFS) from end of one course of therapy for patients in remission was also similar between the three genotypes (p = 0.78). Multivariate analyses that adjusted for study assignment, age, gender, race, and WBC also suggested XPD genotypes did not have different OS or EFS.

There was no difference in treatment related mortality (TRM) from study entry between different genotypes (18 ± 6% in AA vs. 16 ± 5% in AC vs. 12 ± 8% in CC patients at 5 years; p = 0.43) (Figure 3). Relapse rates (RR) from end of one course of therapy for patients in remission were also similar; 40 ± 8% in XPD751AA vs. 42 ± 8% in 751AC vs. 39 ± 14% in 751CC patients at 5 years (p=0.92) (Figure 4). Thus, XPD genotype was not significantly associated with either resistant disease or treatment-related toxicity.

Discussion

Pharmacogenetic polymorphism and variations in response to damage induced by chemotherapy are being intensively investigated as causes of differential susceptibility to leukemogenesis and differential response to therapy.[26,27,28] When investigating the clinical consequences of human polymorphism, it is important to target polymorphisms that likely change protein function and occur at significant frequencies in the population. Spitz et al studied the functional consequences of the XPD Lys751Gln polymorphism among lung cancer patients and healthy controls. They reported that the variant Gln751Gln genotype was consistently associated with the suboptimal DNA repair capacity (DRC). This was determined by assessing the ability of host cells to remove DNA-adducts induced by benzo(a)pyrene, a major constituent of tobacco smoke. This association was statistically significant among the lung cancer cases but not among the healthy controls, indicating a role for XPD in tobacco-related cancers. [29] These data are controversial, however, and others such as Duell et al and Moeller et al reported no significant relationship between XPD Lys751Gln polymorphism and DNA repair

proficiency.[30,31] These conflicting results have led to suggestions that functionality of the codon 751 polymorphism may be exposure- and pathway-specific, affecting both DNA repair and cell death.[32] Consistent with a role for XPD in cell death, P53-mediated apoptosis is attenuated in XPD mutated fibroblasts.[33,34] Furthermore, P53 interacts directly with the carboxy terminus of XPD, which includes the polymorphic codon 751 residue. [32]

A previous report of adult subjects showed that XPD751 genotype influenced susceptibility to therapy-related leukemia, but not de novo AML.[18] In agreement with this, in this pediatric study we found no influence of XPD751 genotype on susceptibility to de novo AML in children. It should be noted that in the present pediatric study focused on de novo and not therapy-related AML.

There is evidence that DNA repair (NER) protects against mutagenicity and toxicity by removing deleterious DNA lesions from the genome, including those induced by chemotherapy.[35,36,37,38] Because increased DNA repair plays an important role in resistance to platinum based compounds, Park et al evaluated effect of XPD Lys751Gln polymorphism on outcome of 73 patients treated with 5-fluorouracil(5-FU)/oxaloplatin for metastatic colorectal cancer. Their results showed a significant association between response to 5-FU /oxaloplatin and the XPD Lys751Gln polymorphism. Patients with Lys/Lys genotype had the longest median survival and those with Gln/Gln genotype were 6-12 times more likely to have progressive disease.[39]

Allan et al evaluated the association of XPD Lys751Gln polymorphism with outcome following chemotherapy for AML in 341 elderly patients (> 60 years of age) entered into the United Kingdom Medical Research Council (MRC) AML 11 trial. [18] In this study XPD 751 glutamine homozygotes had significantly inferior DFS at one year compared with patients with other genotypes. The authors postulated 2 general mechanisms by which the XPD codon 751 variant may modulate myeloid cell death in response to chemotherapy: either via a direct role for XPD in signaling cell death, or indirectly via XPD repair of protoxic DNA lesions.

In contrast to the findings of Allan et al, our study did not demonstrate any differences in outcome of AML therapy in children with different XPD751 genotypes. It is possible that children with AML differ from adults in terms of the biology of their disease – e.g. studies show that older adults have increased frequency of adverse cytogenetic features compared to children.[40,41] Also, over time adult patients have more opportunity to accumulate additional genetic insults (secondary hits), with perhaps increased susceptibility to develop cancers that are more resistant to therapy. Outcomes for treatment of adult AML are commonly inferior to those reported in pediatric series.[42,43,44,45] Also, association studies involving genetic polymorphisms need to be interpreted cautiously in the context of differences in study or population variables. For example compared to children, older adults have poorer tolerance of combination chemotherapy regimens leading to the use of less intensive treatment protocols, as well as increased levels of primary drug resistance associated with over expression of P-glycoprotein (P-gp). Adults in the study by Allan et al received chemotherapy agents

(daunomycin, cytosine arabinoside, thioguanine, etoposide) broadly similar to those received by the children in our study, but it is possible that the effect of XPD polymorphism is regimen specific. A subset of patients in the adult study received an alkylating agent (cyclophosphamide) in post-remission therapy in contrast to our pediatric study, and half were randomized to interferon-α, either of which may have influenced the results. Progress in AML therapy in children has largely been made by aggressive intensification of chemotherapy. It is also possible that intensification of chemotherapy in children can overcome a marginal modulating effect of XPD genotype. Additionally, this XPD variant may be of functional importance in children with AML when combined with other XPD variants, or polymorphic alleles of other DNA repair genes. Mechanistic studies further defining the functionality of XPD polymorphisms will help clarify the importance of variants at this site.

References:

1. Sancar A., and Tang M.S. Nucleotide excision repair. Photochem. Photobiol. 1993; 57:905-921.

2. Eveno, E., Bourre, F., Quilliet, X., et al. Different removal of ultraviolet photoaducts in genetically related xeroderma pigmentosum and trichothiodystrophy diseases. Cancer Res. 1995; 55:4325-4332.

3. Hoeijmakers, J.H. Human nucleotide excision repair syndromes: molecular clues to unexpected intricacies. Eur. J. Cancer. 1994; 13:1912-1921.

4. Hoeijmakers, J.H. and Bootsman, D. Molecular genetics of eukaryotic DNA excision repair. Cancer Cells. 1990; 2:311-320.

5. Svejstrup JQ, Vichi P, Egly JM. The multiple roles of transcription/repair factor TFIIH. Trends Biochem Sci. 1996; 21(9):346-50.

6. Lehmann, A.R. The xeroderma pigmentosum group D (*XPD)* gene: one gene, two functions, three diseases. Genes Dev. 2001; 15:15–23.

7. Bergmann, E. and Egly, J. Trichothiodystrophy, a transcription syndrome. Trends Genet. 2001; 17:279–286.

8. Schaeffer, L., Monocollin, V., Roy, R., et al. The ERCC2/DNA repair protein is associated with the class II BTF2/TFIIH transcription factor. EMBO J. 1994; 13:2388–2392.

9. Hoeijmakers JH, Egly JM, Vermeulen W. TFIIH: a key component in multiple DNA transactions. Curr Opin Genet Dev. 1996; 6(1):26-33.

10. Sung P, Bailly V, Weber C, Thompson LH, et al. Human xeroderma pigmentosum

group D gene encodes a DNA helicase. Nature. 1993; 365(6449):852-5.

11. Evans E., Moggs J. G., Hwang J. R., et al. Mechanism of open complex and dual incision formation by human nucleotide excision repair factors. EMBO J. 1997; 16: 6559-6573.
12. Wei, Q., Cheng, L., Amos,C.I., et al. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. J. Natl Cancer Inst. 2000; 92:1764–1772.
13. Mohrenweiser, H.W. and Jones, I.M. Variation in DNA repair is a factor in cancer susceptibility: a paradigm for the promises and perils of individual and population risk estimation? Mutat. Res. 1998; 400:15–24.
14. Conforti-Froes N, El-Zein R, Abdel-Rahman SZ, et al. Predisposing genes and increased chromosome aberrations in lung cancer cigarette smokers. Mutat Res 1997; 379:53–59.
15. Eastmond DA, Rupa DS, Hasegawa LS. Detection of hyperdiploidy and chromosome breakage in interphase human lymphocytes following exposure to the benzene metabolite hydroquinone using multicolor fluorescence in situ hybridization with DNA probes. Mutat Res. 1994; 322:9 –20.
16. Gao WM, Romkes M, Day RD, et al. Association of the DNA repair gene XPD ASP312Asn polymorphism with p53 gene mutations in tobacco-related non-small cell lung cancer. Carcinogenesis. 2003; 24:1671–1676.
17. Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomarkers Prev. 2002; 11:1513–1530.

18. Allan JM, Smith AG, Wheatley K, et al. Genetic variation in XPD predicts treatment outcome and risk of acute myeloid leukemia following chemotherapy. Blood. 2004; 104:3872-3877.

19. Lange BJ, Gerbing RB, Feusner J, Skolnik J, Sacks N, Smith FO, Alonzo TA. Mortality in overweight and underweight children with acute myeloid leukemia. JAMA 2005; 293:203-211.

20. Lange BJ, Dinndorf P, Smith FO, Arndt C, Barnard D, Feig S, Feusner J, Seibel N, Weiman M, Aplenc R, Gebring R, Alonzo T. Pilot study of idarubicin-based intensive timing induction therapy for children with previously untreated acute myeloid leukemia in Children's Cancer Group (CCG) Study 2941. J Clin Oncol 22:150-156, 2004

21. Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. Ann Math Statistics 1947; 18: 50-60.

22. Kaplan EL, Meier P. nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457-481.

23. Greenwood M. The natural duration of cancer. Reports on Public Health and Medical Subjects, 33. London UK, Her Majesty's Stationery Office 1926:1.

24. Peto R, Peto J. Asymptotically efficient rank in variant text procedures. J R Stat Soc. 1972; (A) 135-185.

25. Gray RJ 1988 Gray RJ. A Class of K-sample tests for comparing the cumulative incidence of a competing risk. The Annals of Statistics 1988; 16: 1141-1154.

26. Naoe T, Takeyama K, Yokozawa, T et al. Analysis of genetic polymorphism in NQO1, GST-M1, GST-T1, and CYP3A4 in 469 Japanese patients with therapy-related

leukemia/myelodysplastic syndrome and de novo acute myeloid leukemia. Clin Cancer Res. 2000; 6:4091-4095.

27. Wiemels JL, Smith RN, Taylor GM, et al. Mehtylenetetrahydrofolate reductase (MTHFR) polymorphisms and risk of molecularly defined subtypes of childhood acute leukemia. PNAS. 2001; (98): 4004-4009.
28. Krajinovic M, Labuda D, Mathonnet G, et al. Polymorphisms in gene encoding drugs and xenobiotic metabolizing enzymes, DNA repair enzymes, and response to treatment of childhood acute lymphoblastic leukemia. Clin Cancer Res. 2002; 8(3): 802-10.
29. Spitz, M.R., Wu, X., Wang, Y., et al. Modulation of nucleotide excision repair capacity by XPD polymorphisms in lung cancer patients. Cancer Res. 2001; 61:1354-1357.
30. Duell, E.J., Wienke, J.K., Cheng, T.J., et al. Polymorphisms in the DNA repair genes XRCC1 and ERCC2 and biomarkers of DNA damage in human blood mononuclear cells. Carcinogenesis. 2000; 21:965-971.
31. Moeller, P., Knudsen, L.E., Frentz, G., et al. Seasonal variation of DNA damage and repair in patients with non-melanoma skin cancer and referents with and without psoriasis. Mutat. Res. 1998; 407:25-34.
32. Seker H, Butkiewicz D, Bowman ED, et al. Functional significance of XPD polymorphic variants: attenuated apoptosis in human lymphobtastoid cells with the XPD312 Asp/Asp genotype. Cancer Res. 2001; 61:7430-7434.
33. Wang XW, Vermeulen W, Coursen JD, et al. XPB and XPD helicases are components of the p53-mediated apoptosis pathway. Genes Dev. 1996; 10:1219-

1232.

34. Robles AI, Wang XW, Harris CC. Drug-induced apoptosis is delayed and reduced in XPD lymphoblastoid cell lines: possible role of TFIIH in p53-mediated apoptotic cell death. Oncogene. 1999; 18:4681-4688.

35. Grant DF, Bessho T, Reardon JT. Nucleotide excision repair of melphalan monoadducts. Cancer Res. 2000; 58:5196-5200.

36. Reardon JT, Vaisman A, Chaney SG, Sancar A. Efficient nucleotide excision repair of cisplatin, oxaloplatin, and bis-aceto-amine-dichlororcyclohexylamine-platinum(IV) (JM216) platinum intrastrand DNA diadducts. Cancer Res. 1999; 59:3968-3971.

37. Ziemba A, Derosier LC, Methvin R, et al. Repair of triplex-directed DNA alkylation by nucleotide excision repair. Nucleic Acids Res. 2001; 29:4257-4263.

38. Zheng HY, Wang X, Warren AJ, et al. Nucleotide-excision repair- and polymerase eta-mediated error-prone removal of mitomycin C interstrand cross-links. Mol Cell Biol. 2003; 23:754-761.

39. Park DJ, Stoehlmacher J, Zhang W, et al. A xeroderma pigmentosum group d polymorphism predicts clinical outcome to platinum-based chemotherapy in patients with advanced colorectal cancer. Cancer Res. 2001, 61, 8654-8658.

40. Dastugue N, Payen C, Lafage-Pochitaloff M, et al. Prognostic significance of karyotype in de novo adult myeloid leukemia. Leukemia. 1995; 9:1491-1498

41. Leith CP, Kopecky KJ, Godwin J, et al. Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenetics distinguishes biological subgroups with remarkably distinct responses to standard chemotherapy: a Southwest Oncology Group study. Blood. 1997; 89:3323-3329

42. Rees JKH, Gray RG, Swirsky D, et al. Principal results of the Medical research Council's 8th acute myeloid leukaemia trial. Lancet. 1986; 2:1236-1241

43. Hiddemann W, Kern W, Schoch C, et al. Management of acute myeloid leukemia in elderly patients. J Clin Oncol. 1999; 17:3569-3576

44. Goldstone AH, Burnett AK, Wheatley K, et al. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML 11 trial. Blood. 2001; 98:1302-1311

45. Stone RM**.** The difficult problem of acute myeloid leukemia in the older adult. CA Cancer J Clin. 2002; 52(6):363-71.

Table 1. Patient characteristics for XPD751AA vs. 751AC vs. 751CC genotypes

Characteristic	AA (N=193) N	AA (N=193) %	AC (N=202) N	AC (N=202) %	CC (N=61) N	CC (N=61) %	AA vs AC P	AC vs CC P	AA vs CC P
Age: median & range (yrs)	10.2	(0.15 - 19.5)	9.6	(0.01 - 19.8)	11.0	(0.13 - 20.9)	0.43	0.57	0.98
WBC: median & range	22800	(1000 - 373300)	18650	(1000 - 860000)	18800	(300 - 684000)	0.36	0.53	0.22
Bone marrow blasts %: median & range	70.5	(0 - 100)	70	(1 - 100)	67	(15 - 98)	0.73	0.65	0.48
Study									
CCG-2941	11	6%	18	9%	8	13%	0.30	0.47	0.09
CCG-2961	182	94%	184	91%	53	87%			
Gender									
Male	109	56%	105	52%	36	59%	0.43	0.41	0.84
Female	84	44%	97	48%	25	41%			
Race									
White	116	60%	142	70%	55	90%	0.05	<0.01	<0.001
Black	20	10%	18	9%	0	0%	0.74	0.02	0.01
Hispanic	40	21%	26	13%	5	8%	0.05	0.44	0.04
Asian	7	4%	7	3%	0	0%	0.86	0.36	0.20
Other	9	5%	9	4%	1	2%	0.90	0.46	0.46
Unknown	1		0		0				
FAB									
M0	17	9%	7	3%	2	3%	0.04	1.00	0.26
M1	30	16%	31	15%	9	15%	0.95	0.93	0.97
M2	61	32%	53	26%	18	30%	0.27	0.73	0.86
M4	39	20%	60	30%	19	31%	0.04	0.96	0.11
M5	31	16%	37	18%	9	15%	0.66	0.65	0.95
M6	5	3%	4	2%	1	2%	0.75	1.00	1.00
M7	5	3%	8	4%	3	5%	0.64	0.72	0.40
Other	4	2%	2	1%	0	0%	0.44	1.00	0.58
Unknown	1		0		0				
Cytogenetics									
Normal	28	23%	27	23%	11	31%	0.94	0.48	0.51
t(8;21)	18	15%	18	15%	10	28%	0.90	0.14	0.13
Abn 16	15	13%	10	8%	2	6%	0.42	0.73	0.36
Abn 11	23	19%	26	22%	8	22%	0.67	0.84	0.87
t(6;9)	1	1%	3	3%	1	3%	0.37	1.00	0.41
-7/7q-	6	5%	2	2%	0	0%	0.28	1.00	0.34
-5/5q-	2	2%	2	2%	0	0%	1.00	1.00	1.00
+8	11	9%	7	6%	0	0%	0.48	0.20	0.07
+21	2	2%	0	0%	0	0%	0.50	1.00	1.00
Pseudodiploid	10	8%	15	13%	3	8%	0.37	0.57	1.00
Hyperdiploid	0	0%	7	6%	1	3%	<0.01	0.68	0.23
Hypodiploid	4	3%	1	1%	0	0%	0.37	1.00	0.57
Unknown	73		84		25				
CNS at on-study	8	4%	10	5%	5	8%	0.89	0.35	0.31
Chloroma at on-study	15	8%	26	13%	8	13%	0.13	0.87	0.31
Response at end of first course									

REM	170	90%	165	86%	51	84%	0.30	0.81	0.26
PD	9	5%	15	8%	8	13%	0.31	0.32	0.04
Die	10	5%	12	6%	2	3%	0.86	0.53	0.74
W/D or unevaluable	4		10		0				

Table 2. Allele specific Primers and Probes

Primers:

Forward Primer – CCT TCT CCC TTT CCT CTG TTC T

Reverse Primer – CAC TCA GAG CTG CTG AGC AAT C

Probes:

VIC (wild type) – ATC CTC TTC AGC GTC T

FAM (variant) – TCC TCT GCA GCG TC

Table 3.

Cases versus controls: WHITE, p=0.125; BLACK, p=0.239

	White Cases		White Controls			Black Cases		Black Controls		
XPD751	N	%	N	%	P	N	%	N	%	P
AA	116	37.1	183	42.4	0.167	20	52.6	87	59.6	0.555
AC	142	45.4	194	44.9	0.960	18	47.4	52	35.6	0.254
CC	55	17.6	55	12.7	0.083	0	0	7	4.8	0.348

Figure 1. OS from study entry: XPD751AA vs. AC vs. CC genotypes

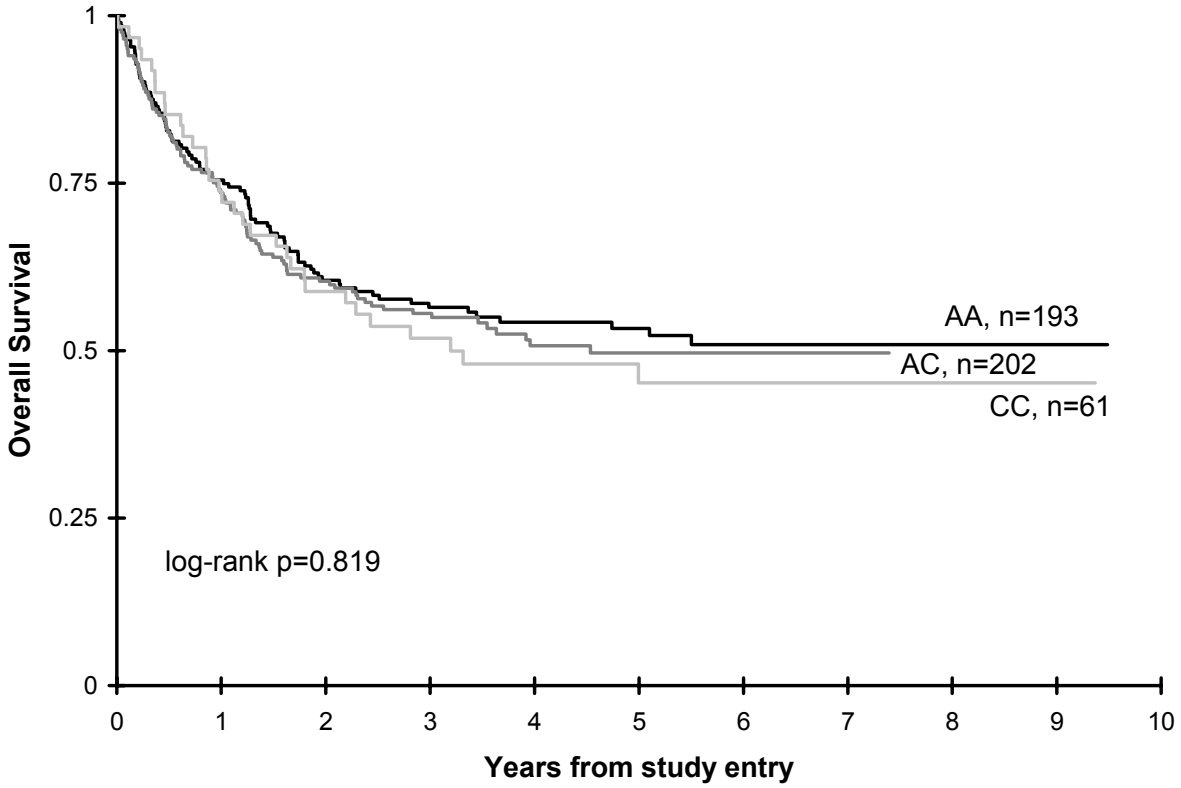

Figure 2. EFS from study entry: XPD751AA vs. AC vs. CC genotypes

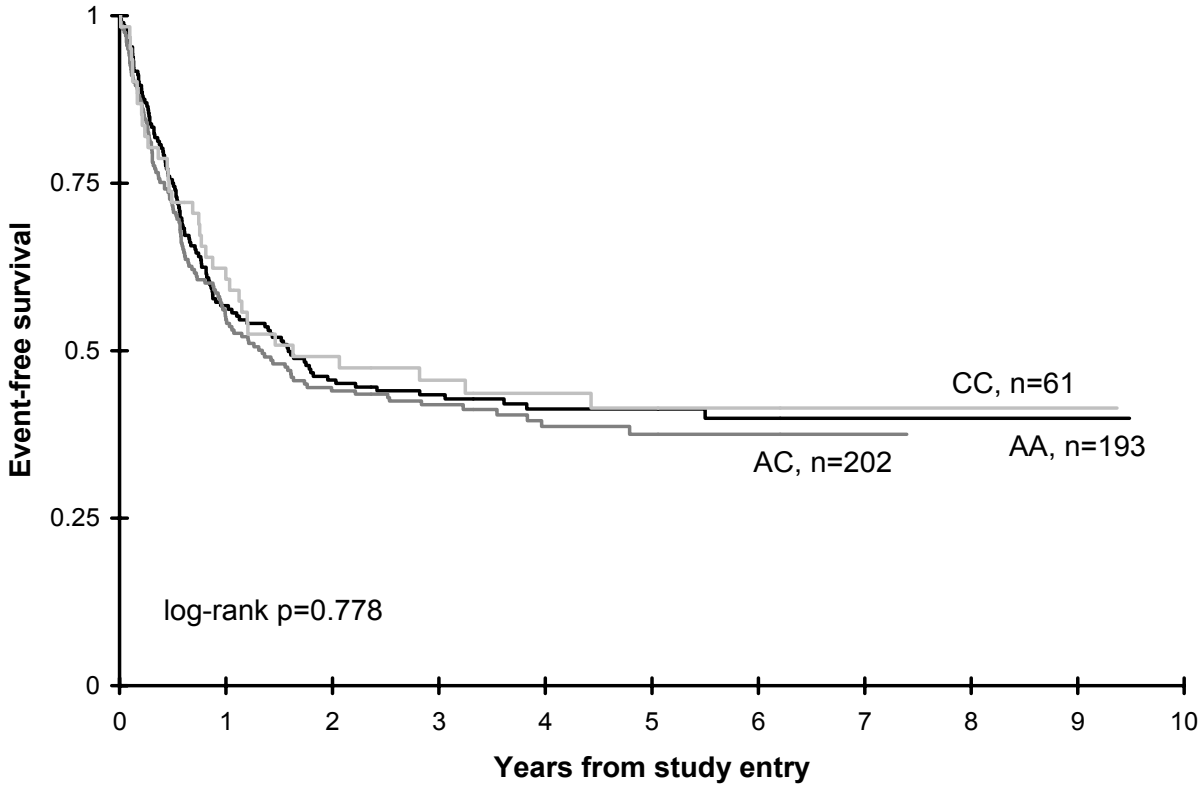

Figure 3. TRM from study entry: XPD751AA vs. AC vs. CC genotypes

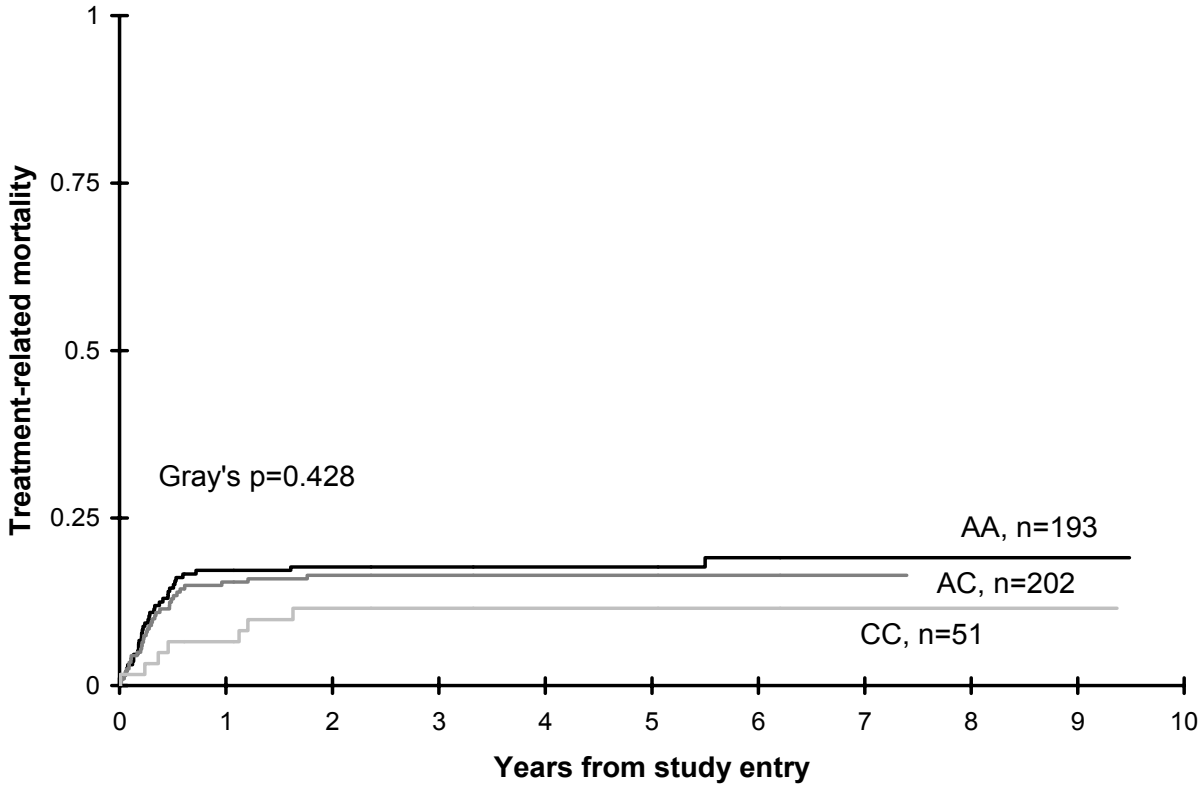

Figure 4. RR from end of one course: XPD751AA vs. AC vs. CC genotypes