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# PROGNOSTIC EFFECT OF GENDER ON OUTCOME OF TREATMENT FOR ADULTS WITH ACUTE MYELOID LEUKAEMIA

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## Abstract

There are conflicting reports in the literature suggesting that one gender or the other has a better survival with acute myeloid leukaemia (AML). This study was done in an attempt to resolve the issue. The effect of gender was examined on 3,546 newly diagnosed patients with AML, including 548 patients with acute promyelocytic leukaemia (APL) enrolled in 10 multi-institutional treatment studies from March 1984 to November 2008. Kaplan-Meier estimates were used to estimate event-time distributions for survival and multivariate models were used to examine the gender effect after adjusting for multiple risk factors. P values were based on 2-sided tests. Non-APL female patients had a significantly better overall but not disease-free survival than males, irrespective of age, initial WBC count, or dose of daunorubicin. No differences were observed for obese or FLT3-ITD + patients. Female APL patients had a significantly better overall and disease-free survival than male APL patients, and differences in survival were greater

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Authorship contributions

PHW conceived and designed the research, contributed patients to the studies and wrote the manuscript. ZS performed the statistical analysis and developed the figures. LDC, JMR, HF, SML, HML, MST and MRL contributed to revision of the manuscript and contributed patients to the studies. EMP performed flow cytometry and other investigations required for study eligibility for each patient on the studies.

Conflicts of interest

The authors declare no competing financial or other interests.

for patients with t(15;17) + other cytogenetic abnormalities compared with those with t(15;17) only. Gender is an independent prognostic variable in patients with AML. Whether these survival differences are due to hormonal, genetic or pharmacokinetic differences between the sexes, or differential toxin exposure such as smoking is unknown. However, the former seems less likely since patient age did not influence the survival advantage for female patients.

### Keywords

Gender; acute myeloid leukaemia; acute promyelocytic leukaemia

There is contradictory information in the literature with respect to the effect, if any, of gender on the outcome of treatment of newly diagnosed patients with acute myeloid leukaemia (AML). While many studies demonstrate a positive effect of female gender on overall survival, some studies conclude that males have superior overall survival compared with females [1]. Furthermore, much preclinical data suggest a positive effect of androgens as well as estrogens on AML pathogenesis [2]. One report [3] showed that in a large randomized study of 330 AML patients, androgen therapy added to standard intensive induction and post-remission therapy significantly improved event-free and overall survival rates for elderly patients with a presenting WBC of ≤ 30,000/μL.

In an effort to resolve the controversy over the effect of gender on outcome in patients with AML, we performed a retrospective study of a large number of patients enrolled in consecutive studies of the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN).

## Study design

### Patients and Methods

We examined the effect of patient self-reported gender on outcome of 3,546 newly diagnosed patients with AML, including 548 with acute promyelocytic leukaemia (APL), enrolled on 10 protocols (E3483, E3489, PC 486, E3993, E4995, E1490, E2491, E3997, E1900 and E3999) of the ECOG-ACRIN Cancer Research Group from March 1984 to November 2008. The treatment details of these studies are detailed in the supplemental table. Baseline characteristics of the patients are presented (Tables 1–3). The median follow-up for patients still alive was 10.7 years. Overall survival (OS) was defined as time from randomization to death from any cause. For patients who achieved CR after induction, disease-free survival (DFS) was defined as the time from documented CR to relapse or death from any cause.

### Statistical analysis

Kaplan-Meier estimates were employed to estimate the event-time distributions for OS and DFS. Multivariate models stratified by protocol and treatment were used to examine the gender effect after adjusting for the following risk factors: age, cytogenetic risk, ECOG performance status (PS), initial white blood cell count (WBC), platelet count, marrow and blood blast counts, and hemoglobin concentration as well as presence or absence of obesity in 2 large studies of non-APL patients. Also, the effect of gender on outcome of patients

who were FLT3-ITD+ or negative (Table 2) was evaluated for non-APL patients enrolled in another large study (E1900). All P values were based on 2-sided tests. We examined the effect of gender across all studies included in this analysis. The log-rank test and multivariate Cox models were stratified by study. The proportion of females enterd in each study ranged from 43.6% to 60%. No significant difference in the distribution of gender was found by study (p=0.33).

## Results

### OS and DFS of non-APL patients (N=2,998)

Table 1 shows the number of patients from each study included in the present analysis. Table II shows the baseline characteristics of the non-APL patients included in the study. The OS of the non-APL patients was moderately but significantly better for female compared with male patients (p<0.001}, (Figure 1A). However, although there was a DFS difference in favor of females, the difference was not significant (Figure 1B). Fig 2 is a forest plot of OS for all patients and various subgroups. Although moderate, the difference in OS (Fig 2) in favor of females is highly significant (HR: 0.85, 95% CI (0.79, 0.93), p= 0.0001. As shown in Table 4, after adjusting for other risk factors in a multivariate model that included gender, age, performance status, initial WBC, blast counts and cytogenetic risk factors, gender was an independent significant variable (p=0.0029) for non-APL patients. A forest plot of DFS showed essentially the same data (data not shown).

Although as stated above, overall there was a significant advantage for female gender in terms of OS, Figure 2 shows that that was not true for every study in the analysis, specifically the smaller studies. The overall female gender advantage was an independent variable irrespective of patient age, WBC, or initial blood and marrow blast counts. Obese patients and patients with FLT-ITD positivity did not demonstrate gender differences in OS.

The female gender advantage for OS was significant for non-APL patients aged < or > 45 years of age (Figures 1C and 1D), and for patients with an initial WBC < or > 10,000/μL (Figures 3A and 3B).

Information on the presence or absence of obesity was available from 2 large studies, E1900 and E3999 and the OS of obese and non-obese non-APL patients was evaluated. There was no difference in overall survival attributable to the gender of 356 obese patients enrolled on the same studies (Figure 4A), however OS of 323 non-obese females was significantly better (p=0.019) than that of 403 non-obese males enrolled in those studies (Figure 4B).

No overall survival difference based on gender was observed in 146 FLT-ITD+ patients enrolled in E1900 (Figure 4C) but of 454 FLT3-ITD-negative patients enrolled in that study, 212 females had a significantly better OS than 242 male patients (Figure 4D)(p=0.034). FLT3-ITD+ males and females had virtually identical OS, both inferior to that of FLT3-ITD-negative patients. FLT3-ITD-positivity obliterated any positive effect of female gender on OS observed in FLT3-ITD-negative patients.

Interestingly, the advantage for females in terms of OS was evident at all 3 daunorubicin doses studied (Figure 5). Fig 5 shows that both genders had better OS with increasing daunorubicin doses and that the improvement in OS for females is greater than that of males.

### OS and DFS of APL patients (N=548)

Figuress 6A and 6B show Kaplan –Meier curves for OS and DFS for APL patients by gender and fig 2 is a forest plot of OS. Females had significantly longer OS compared with males (HR: 0.65, 95% CI (0.52, 0.82, p=0.0004). After adjusting for other risk factors in a multivariate model, females still had a significantly longer OS compared with males (HR: 0.69, 95% CI 0.51, 0.92, p=0.011) (Table 4). Furthermore, unlike non-APL patients in this study, females had a significantly longer DFS compared with males (HR: 0.54, 95% CI (0.41, 0.72, p<0.0001). As shown in Table 5, females had significantly longer DFS compared with males after adjusting for other risk factors in a multivariate model (HR; 0.64,95% CI (0.45, 0.91, p=0.013).

Female APL patients had significantly better OS and DFS than male APL patients irrespective of treatment, but those females who received all-trans-retinoic acid (ATRA) had a greater OS advantage over males than did those females who never received ATRA (Figure 2). APL patients with t(15;17) as the only cytogenetic abnormality had a trend toward better OS for females, but female APL patients with cytogenetic abnormalities in addition to t(15;17) had a significant survival advantage over males (Figures 6C, 6D).

## Discussion

We report here the effect of gender on treatment outcome in a large number of patients with AML or APL determined from a large retrospective study of patients enrolled in ECOG-ACRIN studies over a 24+ year period. We were motivated to do this study by the fact that although most published information suggests an advantage for female gender in outcome of treatment for pediatric ([4–13] non-APL AML and APL patients, some studies, usually small ones, suggest an advantage for male patients [1,14], or no difference in outcome due to gender [15]. One study demonstrated that loss of the Y chromosome in male patients with core binding factor AML resulted in shorter OS [16]. Another study found that RUNX1 mutations are more common in males with AML and that such mutations are highly significantly correlated with inferior overall survival compared with females [17]. These studies demonstrate that some genetic mutations and chromosomal deletions with poor prognostic significance may occur more frequently in males.

In the present study, which is the largest study to date on the effect of gender on outcome of adults with AML or APL, we demonstrate that females with AML other than APL and those with APL have a greater OS compared with males when treated with modern treatment regimens. Females with APL also have greater DFS compared with males when so treated. These effects of gender on outcome were observed irrespective of age at diagnosis which suggests that menopausal status is not responsible for these observations. Initial WBC and other presenting factors were also shown to not influence the effect of gender on outcome. Interestingly, gender did not influence outcome in patients who were FLT3-ITD+ or those who were obese. Obesity is a well known negative prognostic factor for patients

with AML, especially those with APL [18,19] and those AML patients in the European LeukemiaNet {ELN) favorable subgroup [20]. The influence of female gender on outcome of patients with APL was greater in those patients who received ATRA than in those treated with chemotherapy only. Female APL patients with t(15;17) plus additional cytogenetic abnormalities had a significant OS advantage compared with male such patients. The explanation(s) for these findings is unclear.

Some have suggested that whatever gender differences in outcome may have been evident in the past, modern therapy has obliterated them. That does not appear to be the case in the present study since an advantage in OS for females was clearly observed in our most recent study of induction therapy with daunorubicin, 90 mg/m$^2$ daily X 3 during induction therapy (Figure 5).

The observation that female gender is associated with a more favorable outcome than male gender in patients with AML or APL is supported by data from transplant studies. In 2 major studies [21,22] males who received donor hematopoietic stem cells from female siblings had a significantly better outcome than males who received male sibling donor cells. It is hypothesized that in a female to male transplant donor T-cells specific for recipient minor histocompatibility antigens encoded by Y chromosome genes may contribute to a graft-versus-leukemia effect [21]. However, this theory is questioned by a study in which male recipients of HLA-identical female donor cells or donor cells from a male HLA-matched unrelated donor had essentially the same outcome [23].

The data in the literature on sex hormone interaction on leukemia cell lines and models of human disease are confusing. For instance, with respect to androgens, well conducted studies demonstrate prolongation of the life of mice with leukemia, inhibition of proliferation of certain leukemia cell lines in vitro, high-affinity androgen binding sites on a minority of patient-derived myeloid leukemia cells and other positive antileukemic effects [2]. On the other hand, estrogen selective induction of apoptosis of myeloid leukemia cells was demonstrated in a xenograft model [24]. Furthermore, pituitary-secreted gonadotropins have been shown to stimulate migration, adhesion and proliferation of several human myeloid leukemia cell lines [25]. Also of interest is the fact that certain testis-specific genes demonstrate a gender-dependent expression pattern in AML blast cells [26].

Androgen therapy can improve the OS of AML patients >65 years of age with an initial WBC of <30,000/μL according to a recent report [3]. Figure 7 shows that in our patients with these features there is no significant difference in OS between males and females with these characteristics (p=0.19). It therefore seems unlikely that exogenous androgen administration would be advantageous to either gender. Indeed, there are theoretical reasons why it may be harmful. Androgens may facilitate the entry of certain viruses into cells [27,28] and in at least one animal species AML may be caused by a retrovirus [29], and some data suggest that human AML may be caused by a retrovirus as well [30]. If such is the case, one might postulate that males do more poorly with AML than females due to androgen enhancement of the activity of an etiologic agent. Furthermore, smoking which is associated with increased risk of AML as discussed below, upregulates the androgen pathway and is known to increase susceptibility to certain viruses [31].

This study confirms and extends our earlier observation that female gender provides a survival advantage for patients with AML [32], but the explanation for this finding is elusive. One study suggested that the explanation may be that more males than females have unfavorable cytogenetics [33] but that suggestion has not been confirmed.

Another possible explanation for our observations is that the sexes metabolize the drugs commonly used for AML differently. There are very few data in the literature on gender effect on the metabolism or pharmacokinetics of anthracyclines or cytarabine. In one small study [34] males were found to have significantly higher clearance of doxorubicin, an anthracycline analog of daunorubicin, than females. These data suggest that males have less drug exposure than females given the same dose. On the other hand, in another small study there was no correlation between daunorubicin reductase level in leukemic cells from patients with AML, and gender [35]. Pharmacology studies correlated with gender should be explored further in an effort to determine whether significant pharmacologic differences between the genders might explain our results. Recently it has been reported that smoking is associated with an increased risk for AML [36] and shorter survival of patients with AML [37]. In the latter study significantly fewer female patients were smokers. These data suggest that the female survival advantage demonstrated in the present study may be due in whole or in part to difference in smoking habits.

We report here that female gender confers a survival advantage on patients with AML, including APL, but we do not identify the mechanism(s) responsible for this observation. Explanations at a molecular level have been offered for a female survival advantage in some other neoplasms, most recently for malignant glioma [38]. Others may wish to explore whether similar mechanisms are at play in AML.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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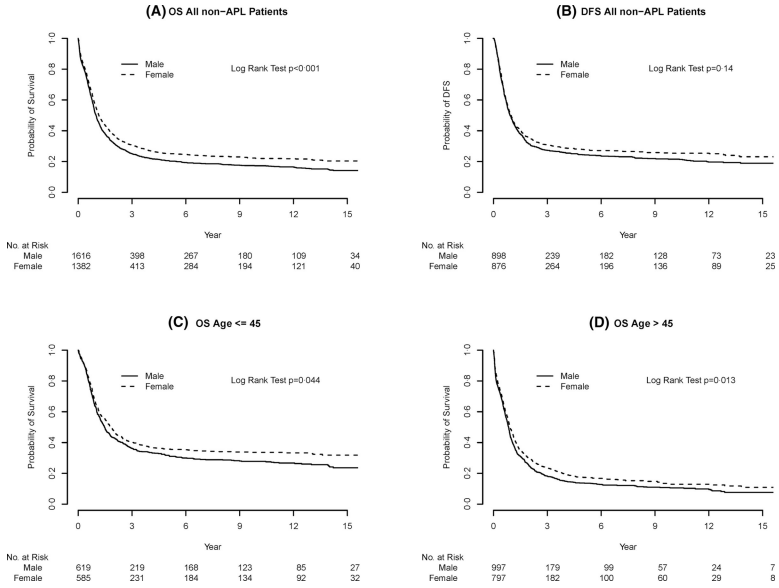


**Figure 1.**

Survival of patients treated for AML by gender. (A) OS of all non-APL patients. (B) DFS of all non-APL patients. (C) OS of non-APL patients <= 45 years of age. (D) OS of non-APL patients > 45 years of age.

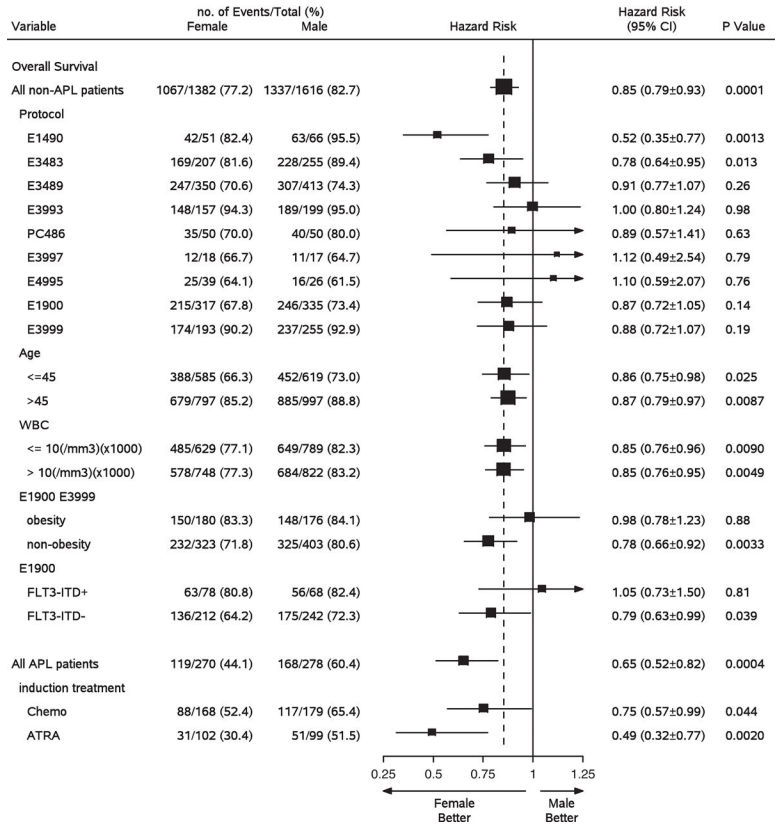


**Figure 2.**

Forest plot of hazard ratios (female/male) subgroup analysis for OS of non-APL and APL patients.

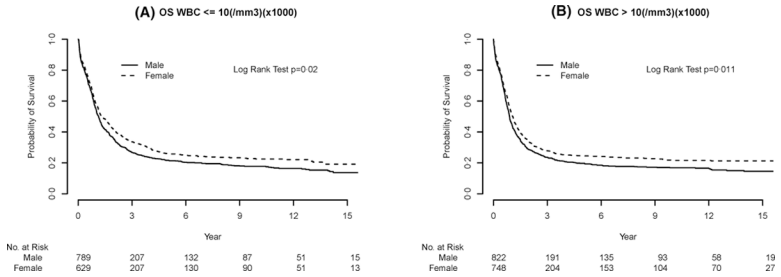


**Figure 3.**

OS of non-APL patients by gender according to initial WBC. (A) WBC <= 10,000/μL. (B) WBC > 10,000/μL.

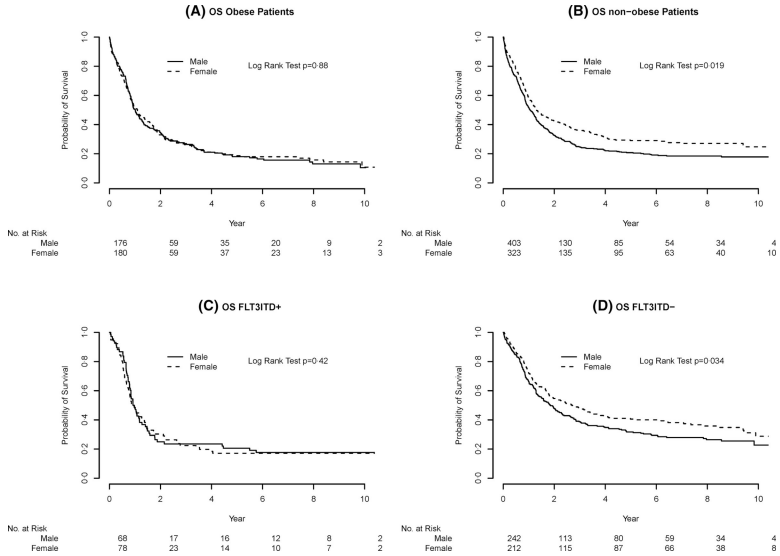


**Figure 4.**

OS of non-APL patients by gender according to other characteristics. (A) Obese patients on studies E1900 and E3999. (B) Non-obese patients on studies E1900 and E3999. (C) FLT3-ITD+ patients on study E1900. (D)FLT3-ITD-negative patients on study E1900.

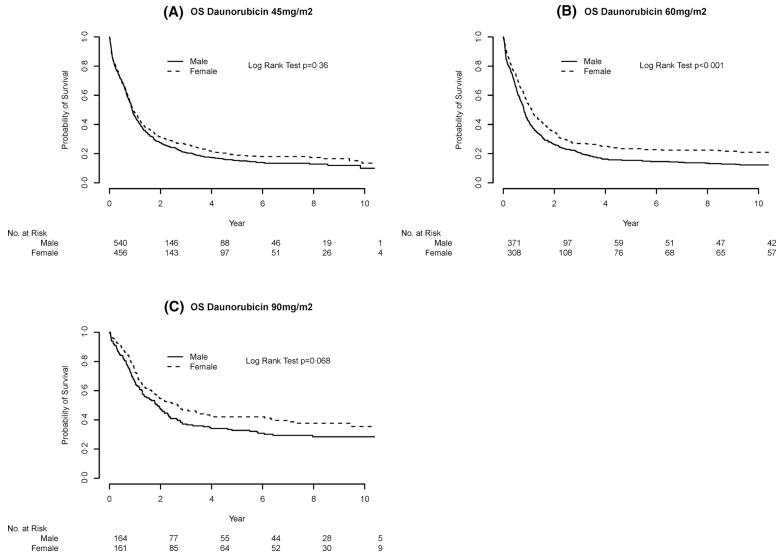


**Figure 5.**

OS of patients treated with various doses of daunorubicin during induction. (A) 45 mg/m$^2$, (B) 60 mg/m$^2$, and (C) 90 mg/m$^2$. Both genders had better OS with increasing doses of daunorubicin, but females better OS than males with the 2 higher doses.

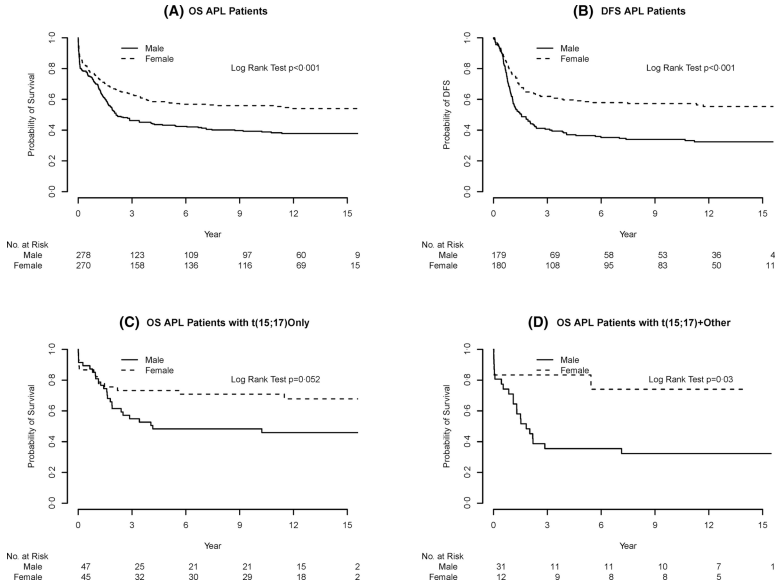


**Figure 6.**

Survival of patients treated for APL by gender. (A) OS of all APL patients. (B) DFS of all APL patients. (C) OS of patients with t(15;17) as the only cytogenetic abnormality. (D) OS of patients with cytogenetic abnormalities in addition to t(15;17).

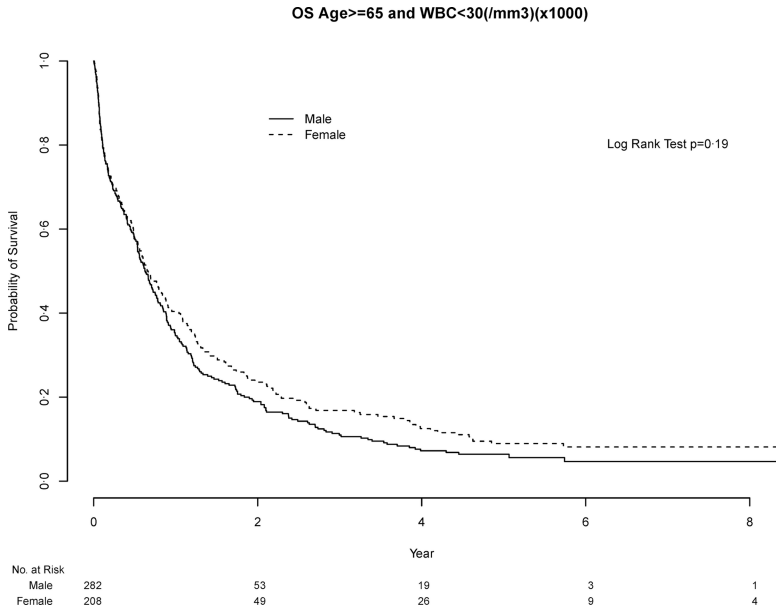


**Figure 7.**

OS of non-APL patients >65 years of age and initial WBC <30,000/μL reported to benefit from androgen therapy [3], by gender.

**Table 1.**

Number of patients from each study

| Study | No.# APL* | M/F+ | No.# Non-APL | M/F | Total |
|---|---|---|---|---|---|
| E1490 | 7 | 5/2 | 117 | 66/51 | 124 |
| E1900 | 5 | 0/5 | 652 | 335/317 | 657 |
| E2491 | 401 | 207/194 | 0 | 0/0 | 401 |
| E3483 | 59 | 27/32 | 462 | 255/207 | 521 |
| E3489 | 44 | 23/21 | 763 | 413/350 | 807 |
| E3993 | 7 | 6/1 | 356 | 199/157 | 363 |
| E3997 | 1 | 0/1 | 35 | 17/18 | 36 |
| E3999 | 1 | 1/0 | 448 | 255/193 | 449 |
| E4995 | 1 | 0/1 | 65 | 26/39 | 66 |
| PC486 | 22 | 9/13 | 100 | 50/50 | 122 |
| TOTAL | 548 | 278/270 | 2998 | 1616/1382 | 3546 |

*APL, acute promyelocytic leukemia

+M/F, number of males/number of females

#No. indicates numbers of patients in the present analyses.

**Table 2.**

Pre-treatment and other characteristics of non-APL patients

| Characteristic | Male | Female | P-value |
|---|---|---|---|
| ***Pretreatment*** | | | |
| Age (yrs) | 52 (15–81)* | 49 (15–93)* | 0.02 |
| WBC/μL | 10.6 (0–30.2) | 12.3 (0–435) | 0.67 |
| Hemoglobin, g/dl | 9.2 (0–40) | 9.1 (2–29) | 0.01 |
| Platelet count/μL | 50 (0–1660) | 58 (0–999) | 0.02 |
| Blood blasts, % | 27 (0–99) | 30 (0–99) | 0.13 |
| Marrow blasts, % | 65 (1–100) | 66 (1–100) | 0.31 |
| Cytogenetics | | | 0.24 |
| Unknown | 649 (40.2%) | 557 (40.3%) | |
| Favorable | 129 (8.9%) | 101 (7.3%) | |
| Unfavorable | 320 (19.8%) | 244 (17.7%) | |
| Intermediate | 445 (27.5%) | 418 (30.2%) | |
| Indeterminate | 73 (4.5%) | 62 (4.5%) | |
| Obese | 176 | 180 | 0.06 |
| Not Obese | 403 | 323 | |
| FLT3-ITD+ | 68 | 78 | 0.16 |
| FLT3-ITD-negative | 242 | 212 | |
| ECOG Performance status | | | 0.86 |
| 0–1 | 1362 (84.2%) | 1171 (84.6%) | |
| ≥ 2 | 238 (14.9%) | 201 (14.7%) | |
| Unknown | 16 (1.0%) | 10 (0.7%) | |
| *Other* | | | |

*Numbers in gender columns are medians (ranges).

**Table 3.**

Pretreatment and other characteristics of APL patients

| Characteristic | Male | Female | P-value |
|---|---|---|---|
| *Pretreatment* | | | |
| Age, yrs. | 40.5 (1–81) * | 35.0 (1–81) * | 0.02 |
| WBC/μL | 2.8 (0–550) * | 30.0 (0–509) * | 0.31 |
| Hemoglobin, g/dl | 9.4 (2–16) * | 8.9 (4–94) * | 0.58 |
| Platelets, μL | 34 (1–600) * | 36.5 (9–587) * | 0.12 |
| Blood blasts, % | 10.0 (0–99) * | 11.0 (0–99) * | 0.60 |
| Marrow blasts, % | 35.0 (1–99) * | 44.5 (1–99) * | 0.22 |
| Cytogenetics | | | 0.02 |
| t(15;17) only | 47 | 45 | |
| t(15;17)+ other | 31 | 12 | |
| ECOG Performance score | | | 0.95 |
| 0–1 | 223 (80.2%) | 216 (80.0%) | |
| ≥ 2 | 52 (18.9%) | 51 (19.1%) | |
| Unknown | 3 (1.1%) | 3 (1.1%) | |
| *Other* | | | |
| Transplant yes/no | | | 0.02 |
| yes | 8 (2.9%) | 19 (7.0%) | |
| no | 270 (97.1%) | 751 (93.0%) | |

* Numbers in gender columns are medians (ranges).

**Table 4.**

Overall survival results from multivariate models

| Parameter | HR | 95% CI | P-value |
|---|---|---|---|
| ***Non-APL patients*** | | | |
| Gender | 0.875 | 0.802–0.956 | 0.0029 |
| Age | 1.021 | 1.016–1.025 | <.0001 |
| ECOG PS ≥2 vs. 0–1 | 1.226 | 1.085–1.386 | 0.0011 |
| WBC | 1.003 | 1.002–1.004 | <.0001 |
| Hemoglobin | 0.984 | 0.962–1.006 | 0.1456 |
| Platelet count | 1.000 | 1.000–1.001 | 0.9361 |
| Marrow % blasts | 1.000 | 0.998–1.002 | 0.8964 |
| Blood % blasts | 1.002 | 1.001–1.004 | 0.0093 |
| Cytogenetics: | | | |
| Missing vs. not | 1.776 | 1.542–2.046 | <.0001 |
| Indeterminate vs. Unfavorable | 0.543 | 0.436–0.678 | <.0001 |
| Favorable vs. Unfavorable | 0.331 | 0.266–0.411 | <.0001 |
| Intermediate vs. Unfavorable | 0.455 | 0.401–0.518 | <.0001 |
| ***APL Patients*** | | | |
| Gender | 0.686 | 0.513–0.917 | 0.0110 |
| Age | 1.014 | 1.006–1.022 | 0.0010 |
| ECOG PS ≥2 vs. 0–1 | 1.321 | 0.937–1.862 | 0.1117 |
| WBC | 1.002 | 1.000–1.004 | 0.0347 |
| Hemoglobin | 0.988 | 0.917–1.065 | 0.7551 |
| Platelet count | 1.002 | 0.999–1.006 | 0.1375 |
| Marrow % blasts | 1.001 | 0.996–1.006 | 0.6836 |
| Blood % blasts | 1.009 | 1.004–1.015 | 0.0004 |

Age, WBC, platelets, hemoglobin, marrow and blood blasts were included as continuous variables in the model. CI indicates confidence interval; HR indicates hazard ratio.

**Table 5.**

Disease-free survival results from multivariate models[#]

| Parameter | HR | 95% CI | P-value |
|---|---|---|---|
| ***Non-APL Patients*** | | | |
| Gender | 0.902 | 0.803–1.013 | 0.0814 |
| Age | 1.012 | 1.006–1.018 | <.0001 |
| ECOG PS ≥2 vs. 0–1 | 0.995 | 0.839–1.193 | 0.9570 |
| WBC | 1.002 | 1.001–1.004 | 0.0008 |
| Hemoglobin | 0.985 | 0.955–1.015 | 0.3145 |
| Platelet count | 0.999 | 0.998–1.000 | 0.1100 |
| Marrow % blasts | 1.001 | 0.998–1.003 | 0.5490 |
| Blood % blasts | 1.001 | 0.998–1.004 | 0.2118 |
| Cytogenetics: | | | |
| Missing vs. not | 1.706 | 1.392–2.092 | <.0001 |
| Favorable vs. unfavorable | 0.371 | 0.286–0.480 | <.0001 |
| ***APL Patients*** | | | |
| Gender | 0.639 | 0.449–0.908 | 0.0126 |
| Age | 0.998 | 0.988–1.008 | 0.6798 |
| ECOG PS≥2 vs. 0–1 | 0.911 | 0.583–1.425 | 0.6832 |
| WBC | 1.003 | 1.000–1.006 | 0.0924 |
| Hemoglobin | 1.055 | 0.963–1.155 | 0.2534 |
| Platelet count | 1.002 | 0.997–1.007 | 0.3753 |
| Marrow % blasts | 1.003 | 0.997–1.009 | 0.2924 |
| Blood % blasts | 1.009 | 1.002–1.015 | 0.0069 |

Age, WBC, platelets, hemoglobin, marrow and blood blasts were included as continuous variables in the model. Abbreviations are explained in Table 4.