A RANDOMISED COMPARISON OF CPX-351 AND FLAG-IDA IN HIGH RISK ACUTE MYELOID LEUKAEMIA. RESULTS FROM THE NCRI AML19 TRIAL

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Background

Liposomal daunorubicin and cytarabine (CPX-351) has shown a survival advantage for older patients (>60years) with secondary AML compared to 3+7 chemotherapy however in younger patients there is a lack of randomised evidence for benefit. We have previously reported improved survival with FLAG-Ida treatment as treatment intensification for younger patients identified with high risk (HR) AML following induction therapy and for patients with secondary AML (Burnett AK et al. Leukemia. 2018 Dec;32(12):2693-2697) and considered this regimen an appropriate comparator for trials in younger patients.

Aims

We compared CPX-351 with FLAG-Ida in a randomised fashion in patients who were either HR at trial entry based on cytogenetics or identified as HR following induction or at relapse.

Methods

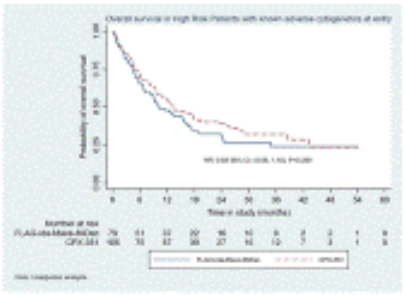
The AML19 trial (ISRCTN78449203) randomised CPX-351 vs FLAG-Ida in 635 patients mainly <60 years with HR AML or MDS (>10% blasts) (median age 53.6 yrs). Three groups of HR patients were randomised 2:1 in favour of CPX with the aim of proceeding to allogeneic transplant. Group 1 (n=195) had known adverse risk cytogenetics (Grimwade et al, Blood 2010,116, 354) and were randomised at diagnosis between 4 courses of CPX-351 and 2 courses of FLAG-Ida followed by MACE/MidAC consolidation. Group 2 (n=263) were HR by validated risk score, had *FLT3*-ITD without an *NPM1* mutation, had refractory disease and were randomised after induction course 1. Group 3 (n=177) were randomised after course 2 if they had persisting MRD at the time of relapse. Here we present results for Group 1. Group 1 was not powered to claim statistical significance; therefore, these results are intended to be exploratory and hypothesis generating.

Results

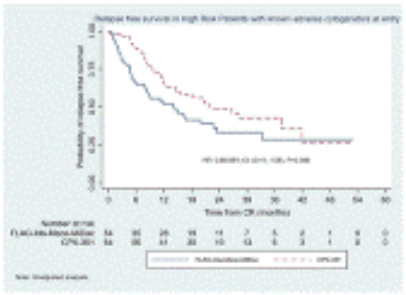
Group 1 included 49.2% with de novo AML 20.3% patients with secondary AML and 30.5% with HR MDS.

The Overall response rate(CR/CRi) was 64.8% for CPX-351 and 74.4% for FLAG-Ida (univariate OR:0.57, 95%CI 0.30-1.10, p=0.09). Overall survival (OS) at 3 years was 32% and 24%, median OS was 13.3 months vs 10.2 months (univariate HR:0.83, 95%CI 0.58-1.18, p=0.3) for CPX -351 and FLAG-Ida respectively (Figure 1a). Event free survival (EFS) was not significantly different (HR:0.91 95%CI: 0.50-1.64, p=0.76). Relapse free survival (RFS) at 3 years was 43% and 28%, median RFS was 22.1 months vs 14 months (univariate HR:0.66, 95%CI 0.41-1.06, p=0.09) for CPX -351 and FLAG-Ida respectively (Figure 1b). RFS was significant when adjusting for NPM1 mutation status or FLT3 mutation status using multivariable cox regression model with RFS being better with CPX-351 compared to FLAG-Ida (HR:0.58, 95% CI0.36-0.95, p=0.03). Median duration of remission favoured CPX and was 319.5 days vs 167 days (p=0.046) for CPX vs FLAG-Ida respectively. Haematological toxicity was greater in course 1 with CPX-351 with platelet recovery to $100x10^9$/L at 34.5 days versus 29 days (p<0.001) and neutrophil recovery to $1.0x10^9$/L at 32 days vs 30 days.(p=0.12). Day 30 and day 60 mortality were not significantly different between arms with 4.8% vs 7.3% (p=0.46) and 12.4% vs 11.0% (p=0.77) for CPX-351 and FLAG-Ida respectively.Compliance was better with CPX-351 with 90.7% vs 83.0% receiving the scheduled course 1 dose. More patients receiving CPX-351 were transplanted (50.5% vs 41.5%) with the median number of courses given prior to transplant 2 in both arms.

1a)



1b)



Conclusion

In patients with adverse cytogenetics CPX-351 did not improve response, OS or EFS compared to FLAG-Ida but was associated with better duration of remission and RFS. Further follow-up is needed to determine the clinical significance of those differences.