

Background: AML is a heterogeneous disease based on genetic characteristics with impact on prognosis. So, it becomes necessary to treat patients according to risk-adapted therapies.

Aims: To analyze the results of intensive induction and post-remission treatment in 868 patients with the novo AML enrolled into the CETLAM-03 trial between 2003 and 2012 with a prolonged follow-up (results reported at 10 years).

Methods: Patients received 1 or 2 induction chemotherapy courses of IDICE-G (idarubicin, intermediate cytarabine (IDC), VP-16 and priming with G-CSF) followed by mitoxantrone and IDC as consolidation therapy. Further treatment was assigned according to the CETLAM risk groups as follows: Favorable risk (FR) defined as favorable cytogenetics according to MRC: autologous stem cell transplantation (ASCT) if leukocyte index [LI=leucocytes x (BM blasts/100)] ≥ 20 or high dose cytarabine (HDAC) (one course) if LI < 20 . Intermediate risk (IR), defined as patients in CR after a single induction course, $< 50 \times 10^9/l$ white blood cells at diagnosis, normal karyotype and absence of FLT3 internal tandem duplication (FLT3-ITDwt) and no MLL rearrangement: ASCT. Adverse risk (AR), patients not included in FP or IP: ASCT or allogeneic stem cell transplantation (allo-SCT) depending on donor availability (HLA-identical sibling or unrelated donor if high risk of relapse).

Results: There were enrolled 868 patients. Median age was 53 years-old (16-70). According to MRC cytogenetics, available in 802 patients, 99 belonged to the favorable (12%), 581 (73%) to the intermediate and 122 (15%) to the adverse groups. 66 patients with no metaphases. FLT3-ITD was present in 128 patients with normal karyotype (36%). Four patients died before treatment and 864 patients received induction therapy. 77% of patients achieved a CR (88% with a single course), 11% were refractory and 12% died during induction. CR rate was 92% in CBF leukemia, 91% in NPM1 mutation without FLT3-ITD, 77% in intermediate cytogenetic and no mutations, 74% if FLT3-ITD, 70% in adverse cytogenetics and 62% if monosomal karyotype was present ($p < 0.001$). The multivariate analysis showed that mutational status (adverse cytogenetics, FLT3-ITD and absence of NPM1 mutation) had an adverse impact on CR achievement. Overall survival (OS), event free survival (EFS) and cumulative incidence of relapse (CIR) of the whole series at 10 years were: $36 \pm 2\%$, $29 \pm 2\%$ and $44 \pm 5\%$ respectively. Post-remission results of OS, EFS and CIR according to the different CETLAM risk groups at 10 years follow up were: FR ($n=85$, 14%): $85 \pm 4\%$, $70 \pm 6\%$ and $22 \pm 1\%$; IR ($n=99$, 17%): $64 \pm 6\%$, $51 \pm 5\%$ and $47 \pm 2\%$; AR ($n=417$, 69%): $41 \pm 3\%$, $33 \pm 3\%$ and $52 \pm 16\%$ respectively. In FR there were no differences in OS, EFS and CIR depending if intention to treat was HDAC or ASCT. In AR statistical differences were observed at 10 years in EFS and CIR when comparing ASCT vs allo-SCT ($27 \pm 4\%$ vs $39 \pm 4\%$, $p=0.026$ and $66 \pm 6\%$ vs $39 \pm 1\%$, $p < 0.001$). In IR intention to treat was ASCT, but in 21% mobilization failed and most of them received HDAC. Forty-nine patients received an ASCT and 21 relapsed, 9 of them were rescued with an allo-SCT.

Summary/Conclusions: In this large cooperative experience CR rate was above 75%, in most cases after a single course. In patients with favorable MRC cytogenetics, the adverse impact of high LI observed in our previous protocol was abrogated with autologous transplantation. In IR group, a remarkable proportion of patients allocated to ASCT had mobilization failure. In HR group, allo-SCT improves the outcome compared to ASCT. In our experience, molecular characterization and MRD studies are helpful to decide post-remission therapy.

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MOLECULAR PREDICTORS OF RESPONSE TO AZACITIDINE THERAPY: THE RESULTS OF THE UK TRIALS ACCELERATION PROGRAMME RAVVA STUDY

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Background: Azacitidine (AZA) represents an important therapeutic advance in patients with acute myeloid leukaemia (AML) and high risk myelodysplasia (MDS) ineligible for intensive chemotherapy. However disease progression appears inevitable and a number of strategies aimed at improving outcome, including co-administration of histone deacetylase inhibitors such as vorinostat (VOR), have been proposed. Leukaemic stem/progenitor cells (LSC) have been postulated to represent a reservoir of resistant disease but the impact of AZA based therapy on LSC numbers has not been studied. An additional factor limiting the rational use of AZA based therapy in AML and MDS is imprecision in the identification of patients likely to achieve a significant clinical benefit and molecular predictors of outcome would improve the rational utilisation of this important new agent.

Aims: We wished to study the impact of AZA based therapy on LSC numbers as well as identify molecular predictors of outcome in patients treated on the recently completed UK Trials Acceleration Programme RAVVA randomised Phase II trial which compared AZA monotherapy with AZA/VOR combination therapy.

Methods: The RAVVA trial randomized 259 adults with AML ($n=217$) and MDS ($n=42$) to receive AZA monotherapy (AZA (75 mg/m²) x 7 days every 28 days) or AZA combined with VOR (300 mg bd days 3-9) po for a minimum of 6 cycles. Next generation sequencing was performed on 42 genes commonly mutated in AML and MDS in 250 patients treated on the RAVVA trial and correlated with response. Separately serial immunophenotypic quantitation of leukaemic stem/progenitor cells (LSC) was performed in 44 patients.

Results: Co-administration of VOR did not increase overall survival (OS) (1 year OS AZA 43% versus 41% $p=0.32$) as previously reported (Blood 2016 Abstract No 1065). The mean number of mutations per patient in the 250 genotyped patients was 3.4. The presence of mutations in CDKN2A ($p=0.0001$), IDH1 ($p=0.004$) and TP53 ($p=0.003$), NPM1 ($p=0.037$) and FLT3-ITD ($p=0.04$) were associated with reduced OS in univariate analysis. In multivariate analysis adjusted for all clinical variables mutations in CDKN2A, IDH1 and TP53 remained predictive of decreased OS. No mutations were associated with improved OS. The presence of ASXL1 ($p=0.035$) and ETV6 ($p=0.033$) mutations were found to be associated with a reduced duration of response. AZA based therapy had no significant impact on LSC numbers in patients who failed to achieve a CR. LSC numbers were reduced but not eradicated in patients achieving a CR and observed to expand at relapse.

Summary/Conclusions: In this, the largest such study reported to date, the demonstration that mutations in CDKN2A, IDH1 and TP53 are associated with a decreased OS in patients treated with AZA not only can inform patient risk stratification but also provides insights into the mechanism of action of AZA. Specifically, the observation that mutations in the cell cycle regulator CDKN2A was associated with a markedly decreased overall survival is consistent with the hypothesis that induction of cell cycle arrest represents at least one of the mechanisms by which AZA exerts an anti-tumour activity. Furthermore our data identify serial quantitation of LSC populations as a potentially important biomarker of response to AZA based therapies which may assist in the evaluation of novel treatment combinations.

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SORAFENIB MAINTENANCE IN FLT3-ITD MUTATED ACUTE MYELOID LEUKEMIA AFTER ALLOGENEIC STEM CELL TRANSPLANT

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Background: The fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutation is a genetic alteration found in approximately 30% of patients with acute myeloid leukemia (AML). Although patients with FLT3-ITD AML achieve remission rates similar to those with FLT3 wildtype status with induction chemotherapy regimens; patients with FLT3-ITD have significantly shorter remission durations and increased rates of relapse. Even though allogeneic SCT improves outcomes, patients still have higher rates of relapse comparatively with poor prognosis post relapse. Sorafenib (SFB) is a TKI with activity against RAF, VEGF and FLT3-ITD and its use as maintenance therapy after allogeneic SCT has been shown as a promising approach to decrease relapse. Several studies report that SFB maintenance post SCT provides durable complete responses; however, there are also descriptions of sorafenib post SCT triggering acute GVHD, cytopenias, rash and diarrhea.

Aims: To assess the outcomes, including progression free survival (PFS) and overall survival (OS), in patients with FLT3-ITD mutated AML who receive SFB maintenance after allogeneic SCT.

Methods: We analyzed adult patients (age ≥ 18) with a diagnosis of FLT3-ITD mutated AML who received an allogeneic SCT between 1/1/2010 and 10/28/16 at our institution. Using a case control analysis and matching patients who received maintenance SFB (maintenance group) with control patients, FLT3-ITD mutated AML who did not receive maintenance post SCT (control group); we matched each case to two control patients accounting for disease status, type of conditioning, donor type, cytogenetic risk factors and age. To be considered as maintenance, SFB had to be started within 101 days of the SCT. To reduce bias from disease risks and transplant-related mortality (TRM), all patients were required to be in complete remission (CR) at study entry - defined as the date of SFB initiation for cases and the same time point after SCT for their matched controls without maintenance. Actuarial OS and PFS were estimated from study entry using Kaplan-Meier method. OS and PFS were compared between cases and controls using log rank test and cox proportional hazards regression analysis. Patient-, transplant- and disease characteristics were compared between cases and controls using chi square and Fisher exact tests.

Results: Among the 214 AML patients with FLT3-ITD mutation that underwent SCT during study period, we identified 13 cases (maintenance) and 26 controls (no maintenance). Median follow-up of survivors were 12 months and 30 months for maintenance and control group respectively. Disease and transplant