Myelodysplastic syndromes - Clinical

S1295

THE ADDITION OF LENALIDOMIDE TO AZACITIDINE IN HIGHER RISK MDS IS DELIVERABLE WITH HIGHER RESPONSE RATES; FIRST ANALYSIS OF THE ALLG MDS4 RANDOMISED PHASE II STUDY

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Background: Azacitidine (AZA) improves OS compared to conventional care regimens in high risk MDS; lower risk MDS obtain clinically relevant responses. Virtually all patients (pts) however ultimately progress with poor prognosis. AZA with lenalidomide (LEN) is a rational combination to investigate for these pts, given the differing mechanisms and established single agent activities. Early phase trials have developed dose and schedule with acceptable toxicity. We present a first analysis of secondary endpoints of the ALLG MDS4 – a randomised phase II study comparing AZA +/- LEN in higher risk MDS and low blast AML.
Aims: 1. assess response rates of AZA and AZA + LEN 2. describe toxicity and deliverability of this combination.
Methods: Thirty centres participated; eligible pts provided informed consent and had low blast, non-proliferative AML, MDS (and RCUD and RARS with at least one clinically significant cytopenia) or non-proliferative CMML, with no prior demethylating agent or IMiD. Pts were stratified according to IPSS, site, diagnosis, and randomised 1:1. Treatment for all pts was AZA 75mg/m^2/d sc 5-2-2 schedule until progression or intolerance; those randomised to combination therapy began LEN at cycle3, 10mg oral D1-21 of each 28d cycle for total 10 cycles with AZA reduced to 5d schedule. Primary endpoint of the study (not analysed to date) is rate of clinical benefit (alive with absence PD) at 12mths. Close-out date for this analysis is Dec31 2013. Responses reported according to IWG criteria and ITT (only 1 pt received no drug).

Table 1.

	AZA (n=77)	AZA+LEN (n=76)
Male	65%	74%
Median age (yrs)	69.1 (42.5-85.9)	71.4 (44.1-87.2)
Median from diagnosis	0.5 (0.1-13.1) yrs	0.4 (0.0-9.4) yrs
ECOG (%)		
0	53%	50%
1-2	47%	50%
Diagnosis		
RARS	8%	4%
RCMD	29%	34%
RAEB-1	14%	13%
RAEB-2	21%	20%
MDS isolated 5q-	3%	1%
AML	10%	14%
CMML	14%	12%
Other	1%	1%
IPSS-R		
Very good	0%	2%
Good	38%	34%
Intermediate	25%	27%
Poor	17%	9%
Very poor	21%	29%
Carrying 5q-	11%	17%
Number cytopenias		
0-1	42%	39%
2-3	58%	61%
Best response		
CR	22%	25%
PR	0	3%
mCR	12%	13%
HI[1]	18% n=14 patients HI-E n=9 HI-P n=5 HI-N n=5	25% n=19 patients HI-E n=10 HI-P n=12 HI-N n=1
SD	29%	21%
PD	4%	5%
Not evaluable/missing	16%	8%

[1]Note patients could have HI response in more than one lineage

Results: Between March 2011 and March 2013 160 pts were randomized; for those continuing on study, only pts ≥12 months from study commencement are included (n=153). Median follow up is 11.7mths (0.7-26.7), median number cycles aza=11 (AZA) v 10 (AZA+LEN); median cycles LEN in combination arm=8. Number AZA cycles dose reduced 2.5% AZA v 2.4% AZA+LEN. A mean of 3.2% per patient LEN cycles were dosed<10mg. See table for baseline data and best responses. ORR (CR to HI) 52% (AZA) v 66% (AZA+LEN) (p=0.08). Median time to first response 2.8mths (AZA) v 2.7mths (AZA+LEN) and to best response 5.5mths (AZA) v 4.7mths (AZA+LEN) (p=0.13). Median PFS 14.4mths (AZA) v 16.4mths (AZA+LEN). Overall rate Gr3+ nonhaem AEs 61% (AZA) v 68% (AZA+LEN); Gr3+ infections 43% (AZA) v 45% (AZA+LEN) including febrile neutropenia 20% both arms. Only other Gr3+ AE >5% pts was raised GGT in AZA+LEN 15%, to be further assessed. Emerging Gr3+ haematologic toxicity: new Hb<80g/L in 41% both AZA and AZA+LEN, neutrophils<1x10^9/L 43% AZA v 49% AZA+LEN, platelets<50x10^9/L in 37% AZA v 40% AZA+LEN. Most haematologic toxicity was seen in the first 2-4 cycles.
Summary and Conclusion: The regimen of concurrent AZA+LEN in pts with higher risk MDS/low blast AML/CMML is deliverable with numerically higher response rates and a trend for shorter time to best response than AZA alone. Toxicity is not excessive, with similar rates of emerging haematologic toxicity and infections. We await main analysis for assessment of primary endpoint of clinical benefit at 12mths treatment and OS.

S1296

ACE-536 INCREASES HEMOGLOBIN LEVELS IN PATIENTS WITH LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROMES (MDS): PRELIMINARY RESULTS FROM A PHASE 2 STUDY

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Background: ACE-536 is a recombinant fusion protein containing modified activin receptor type IIB, being developed for the treatment of anemias due to ineffective erythropoiesis, such as myelodysplastic syndromes (MDS). Patients with MDS often have elevated levels of erythropoietin (EPO) and may be non-responsive/refractory to erythropoiesis-stimulating agents (ESAs). ACE-536 binds to ligands in the TGF-ß superfamily and promotes late-stage erythroid differentiation via a mechanism distinct from ESAs. In a healthy volunteer study, ACE-536 was well-tolerated and increased hemoglobin (Hgb) levels (Attie K *et al.*, Am J Hematol 2014). RAP-536 (murine ortholog of ACE-536) increased Hgb levels and decreased bone marrow erythroid hyperplasia in a mouse model of MDS (Suragani R *et al.*, Blood 2012;120:3796).
Aims: This is an ongoing, phase 2, multicenter, open-label, dose-finding study to evaluate the effects of ACE-536 on anemia in patients with transfusion-dependent (TD) or non-transfusion dependent (NTD) low or int-1 risk MDS. Study outcomes include erythroid response (either Hgb increase in NTD patients or reduced transfusion burden in TD patients), safety, tolerability, PK, and PD biomarkers.
Methods: Inclusion criteria included low or int-1 risk MDS, age ≥ 18 yr, with anemia defined as either Hgb<10.0 g/dL (NTD, defined as<4 units RBCs/8 wks prior to baseline) or ≥4 units RBCs/8 weeks prior to baseline (TD), EPO >500 U/L or non-responsive/refractory to ESAs, no prior azacitidine or decitabine, and no current treatment with ESA, G-CSF, GM-CSF, or lenalidomide. ACE-536 was administered by subcutaneous (SC) injection once every 3 weeks in sequential cohorts (n=3-6) at dose levels ranging from 0.125 to 1.33 mg/kg for up to 5 doses with a 3-month follow-up. Further possible dose escalation and an expansion cohort (n=30) are planned, contingent on periodic safety data review.
Results: Preliminary data were available for 21 patients (12F/9M, 6 NTD/15 TD) enrolled as of 13Feb2014. Median age was 71 yr (range: 27-88 yr). 48% had prior EPO therapy and 19% had prior lenalidomide. Mean (SD) baseline Hgb for NTD patients (n=6) was 9.0 (0.4) g/dL. Mean (SD) units RBCs transfused in the 8 weeks prior to baseline for TD patients (n=15) was 6.2 (2.5) units. Preliminary efficacy data were available for the 15 patients (5 NTD/10 TD) treated in the first 4 cohorts (0.125, 0.25, 0.5, or 0.75 mg/kg). The 5 NTD patients demonstrated dose-dependent increases in Hgb on treatment, with maximum Hgb increase ranging from 0.8 to 3.3 g/dL. The 3 NTD pts in the 0.75 mg/kg group were either ESA refractory or non-responders and had maximum Hgb increases of 1.6, 1.9, and 3.3 g/dL. One NTD patient in this group had a Hgb increase ≥1.5 g/dL sustained for ~15 weeks. Four of the 10 TD patients had a ≥50% reduction in units transfused during an 8-week interval on treatment compared to the 8 weeks prior to treatment, including 1 pt, previously ESA and lenalidomide non-responsive, who was transfusion-free while on study (~22 weeks). Transient increases in reticulocytes and/or neutrophils were observed in some patients. ACE-536 was generally well tolerated. No related serious AEs have been reported to date. No patients discontinued treatment early due to a related AE.

Summary and Conclusion: Based on preliminary data in low or int-1 MDS patients with high baseline EPO levels or lack of response to ESA treatment, ACE-536 administered SC every 3 weeks increased Hgb levels in NTD patients and decreased transfusion requirement in some TD patients, with a favorable safety profile. These data support further evaluation of ACE-536 in patients with MDS.

S1297

MUTATIONAL ANALYSIS AND LONG TERM OUTCOME IN ADVANCED CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML) TREATED BY DECITABINE: AN UPDATE OF THE GFM-CMML-2007 PHASE II TRIAL

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Background: Treatment of advanced CMML remains a challenge with no standard approach except HSCT for a minority of patients. Recently, we and others reported that the hypomethylating agents decitabine (DAC) (Braun et al, Blood 2011) and azacitidine (AZA) (Costa et al, Cancer 2011; Adès et al, Leuk Res, 2013) yield responses ranging from 35 to 45% in this setting.
Aims: Here we analyzed long term outcome in our previously published prospective phase II trial of DAC of advanced CMML (Braun et al, Blood 2011) to identify prognostic factors.
Methods: Between Nov 2008 and June 2009, 39 CMML patients (according to WHO) were included in this clinical trial if they had the following poor prognostic factors, based on a previous prognostic analysis (Wattel et al, Blood 1996): WBC<13G/l and IPSS 1.5; or WBC 13G/l, and two of the following criteria: marrow blasts 5%, Hb<10g/dl, plts<100G/l, abnormal cytogenetics, splenomegaly (SMG) >5cm below costal margin, (SMG>5cm), extra medullary disease (EMD),. Patients received DAC 20mg/m2/d IV for 5 days every 28 days for at least 3 cycles. Response criteria were based on IWG 2006 for patients with WBC<13G/L and also included evolution of WBC, SMG and EMD for patients with WBC ≥ 13 G/L. Data were analyzed 48 months after the last inclusion. For mutational analysis, DNA could be extracted for 37 patients from total BM nucleated cells or PB monocytes, and the following genes studied: ASXL1, CBL, FLT3 mutation and ITD, JAK2, NRAS and K RAS, RUNX1 and TET2. Statistical analysis was performed on Stata SE 10.1 (StataCorp, College Station, TX, USA).
Results: Median age was 71 years M/F: 30/9. 17 patients had CMML 1 and 22 had CMML 2. Nine patients had WBC<13G/l and 30 WBC ≥13G/l. Abnormal karyotype was found in 18 (46.2%) patients, including +8 and -7 in 7 and 1 case, respectively. 15 patients (38.6%) had SMG >5cm and 8 (20.5%) EMD. 58% patients were mutated for ASXL1, 50% for TET2, 31% for RAS (6 NRAS/5 KRAS), 28% for RUNX1, 14% for CBL, 6% for FLT3-ITD, 3% for FLT3 mutation and 3% for JAK2. 58% patients had at least 2 mutations. Overall Response Rate (ORR) was 38.6% with 4 (10.3%) CR, 8 (20.5%) marrow CR and 3 (7.7%) Stable Disease (SD). Median overall survival (OS) was 18 months. WBC, monocytes, Hb level, marrow blast %, SMG or EMD were not significantly prognostic of ORR, response duration or OS. 7/11 (63.6%) RAS mutated patients responded *vs* 8/27 (29.6.%) RAS germline patients (p=0.07). In univariate analysis, RAS mutation, known to have in CMML an unfavorable outcome (at least for NRAS) was associated with better OS (28 *vs* 17 months; p=0.05) and longer response duration (17.8 *vs* 9.2 months, p=0.056) compared to RAS germline. The ORR was 38.1% and 29.4%, and median OS was 18.2 months and 18.4 months in patients with ASXL1 mutations (an overall poor prognostic factor in CMML) and ASXL1 germline patients, respectively (p=0.28 and p=0.36, respectively). 6 patients had prolonged response to DAC of 18, 18, 39, 39, 48 and 58 months respectively. All those 6 patients had ASXL1 mutation, and 4 had concomitant RAS mutation. Another patient was allografted after 6 cycles in CR and was still alive (56+ months).
Summary and Conclusion: In this study of 39 advanced CMML treated with DAC with long term follow up, no conventional prognostic factor of response or survival to DAC emerged, while RAS mutations were associated with a better outcome and ASXL1 had no prognostic value. This possibly suggested a positive effect of DAC in CMML cases with RAS and/or ASXL1 mutation (ie with poor prognostic features), which however requires confirmation in larger series.

S1298

ISOLATED TOTAL MONOSOMY 7 IS ASSOCIATED WITH BETTER PROGNOSIS IN A LARGE COHORT OF MDS PATIENTS COMPARED WITH OTHER ABNORMALITIES OF CHROMOSOME 7- A SINGLE INSTITUTE EXPERIENCE

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Background: Karyotype is a strong independent prognostic factor in myeloid neoplasms and abnormalities of chromosome 7 are the second commonest abnormality in MDS. The differential impact of monosomy 7, del7q (partial loss) and -7 (total loss) on prognosis has been demonstrated and hence incorporated into separate groups in revised IPSS.
Aims: To evaluate the clinical features, treatment and outcome of a large cohort of myelodysplastic syndromes (MDS) and related myeloid neoplasms in patients with cytogenetic aberration involving chromosome 7.
Methods: We retrospectively analysed 168 MDS patients who presented at diagnosis (147) or acquired during follow-up (21) any abnormality of chromosome 7. Patients were diagnosed between 1995 and 2013 at our institution.
Results: Median follow-up was 17 months (mo). Median age at diagnosis was 59 (range 16-91) years; 60% males and 60% more than 60 years. Denovo MDS were 118 (11 RA, 2 RARS, 56 RCMD, 23 RAEB1, 26 RAEB2), 12 had MDS/MPN, 38 AML including 15 secondary to MDS. Overall, 27 MDS/AML were therapy-related. According to IPSS, 15 % were at low, 48% intermediate 1, 19% intermediate 2 and 19% high risk. According to karyotype 4 subgroups were identified: -7 as a single abnormality (39%), -7 associated with other chromosomal aberrations (47%), del(7q) plus other chromosomal aberrations (5%) and patients with add(7) or translocations between 7 and other chromosomes [t(1:7),t(7:17),t(7:21),t(4:7)] (9%). Eighty-six (51%) patients had complex karyotype and 57 (34%) monosomal karyotype. Fifty-seven patients were treated in first line with intensive chemotherapy (IC), 55 with azacytidine (AZA), 32 with other therapies (including lenalidomide, low dose cytarabine) and 23 with best supportive care (BSC). Fifty-four patients underwent allogeneic haematopoietic stem cell transplantation (HSCT); 31 after IC, 15 after AZA and 8 as upfront. Median overall survival (OS) was 19 mo (range 1 to 166) and was significantly affected by karyotype: in isolated -7 group was 27 mo, in -7 plus other abnormalities group 16 mo, in del(7q) group 15 mo and in add(7)/t(7;?) group 8 mo (p<0.016). Moreover, as expected, both complex karyotype (p<0.001) and monosomal karyotype (p<0.002) were poor prognostic factors (median OS 11 and 15 mo, respectively). Patients treated with AZA as front line therapy had a better OS (27 mo) compared to patients who received IC (17 mo), other therapies (19 mo) or BSC (7mo) (p<0.041). As expected, patient who underwent HSCT had a longer survival (25 mo *vs* 18 mo, p 0.022), regardless the pre-HSCT treatment. This could be due of the positive selection of patients who survived and responded to induction therapy. In the MDS subgroup, in addition to the above described prognostic factors, IPSS, WPSS and IPSS-R too were significant outcome predictors (p 0.001). Median progression free survival was 12 mo and was affected by complex karyotype (7 mo *vs* 16 mo, p<0.001), type of 7 abnormality (-7 alone 18 mo, -7 plus other abnormalities 10 mo, del (7) 2mo and add (7)/t (7 ;?) 13 mo, p<0.001), IPSS (p<0.017) but not by therapy. Cumulative incidence of AML was 33% and 40% at 24 and 60 months, respectively.
Summary and Conclusion: In our study isolated -7 had a positive impact on OS compared to other abnormalities of 7, including del7q. This finding is discordant to recently published data, possibly due to fewer patients with isolated del7q, less untreated patients and the younger age of our cohort. AZA seemed to be good treatment option for these patients, even if the better outcome was associated with HSCT, an option for a selected group of patients.

S1299

IDENTIFICATION OF BIOMARKERS WHICH COULD PREDICT THE HEMATOLOGICAL RESPONSE OF NON DEL(5Q) LOW-RISK MDS PATIENTS TREATED BY LENALIDOMIDE ; THE GFM EXPERIENCE

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Background: Lenalidomide (Len) is a successful therapy used to treat anemia of patients with MDS del(5q) in half of the cases. Treatment by Len also induces an erythroid response in ~25% of non del(5q) low-risk or int-1 MDS patients. Len targets the protein Cereblon, a receptor for the substrates of the E3 ubiquitin ligase Cul4A-DDB1-Roc1, including Ikaros (IKZF1) and Aiolos (IKZF3) encoded by the *CRBN* gene.
Aims: Predictive biomarkers of the erythroid response to Len are needed to avoid inappropriate exposition to the risk of severe neutropenia or thrombocytopenia.
Methods: This was investigated in a cohort of 132 non del(5q) MDS patients (IPSS low and int-1), non-responders to a previous treatment by erythropoiesis-stimulating agent (ESA), enrolled in the Groupe Francophone des Myelodysplasies GFM-LenEpo 08 clinical trial (NCT01718379). Patients were randomized to Len 10mg/day 21 days/28 (L-arm) or Len 10 mg/d 21 d/28 plus Epoetin beta (60,000 units/w) (LE-arm) and evaluated after 4 cycles. Ninety-nine/132 patients were enrolled in the biological study including 41 responders and 58 non responders. We have previously reported a significantly HI-E according to IWG2006 in LE-arm (52%) *vs*. L-arm (31%) (p=0.031) (1). Extensive genotyping study of 26 genes (*ASXL1, CBL, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, PHF6, PTPN11,*

RIT1, RUNX1, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, WT1, ZRSR2) was conducted by a NGS approach (AmpliSeq, Life technologies). Mutations were considered as clonal when the VAF was >50%, and subclonal when 5

Results: The most frequently mutated genes were SF3B1 (73%), TET2 (45%?), ASXL1 (20%) and DNMT3A (20%), none of them influencing the response to Len or Len+Epo. Analysis of erythropoiesis based on the ratio of BFU-E/CFU-GM and the GEP signatures delineated two groups of responders patients: (i) a first group with impaired erythropoiesis, as already reported (2) and a second group with still effective erythropoiesis before treatment as assessed by normal or subnormal BFU-E number and the expression of erythroid genes. Using *Gene Set Enrichment Analysis (GSEA), the* comparison of GEP in 24 paired samples obtained before and after 4 cycles of treatment linked the response in L-arm or LE-arm to a signature of 32 up-regulated genes exclusively involved in the immune response. A supervised GSEA analysis of GEP before treatment identified a predictive signature of 36 up-regulated genes mainly involved in translation, cellular division and DNA repair. The basal expression level of 2/36 genes of this signature, further quantified by qPCR in a larger set of patients, was predictive of the response in L-arm or LE-arm ($p<0.001$) with a sensitivity >65% and a specificity >92%. The efficacy of Len or Len+Epo was independent of the basal expression level of CRBN, IKZF1 and IKZF3. However, a A>G polymorphism in the 5'UTR region of *CRBN* gene (rs1672753) was significantly associated with HI-E in the whole cohort (41.5% in responders *vs*. 22.4% in non-responders; p=0.048).

Summary and Conclusion: In conclusion, we have identified three biomarkers predictive of the erythroid response to Len or Len+Epo. 1. A Toma *et al.* Oral Presentation, ASCO Annual Meeting 2013 (#7002), 2. Ebert BL *et al.* PLoS Med. 2008 Feb;5(2):e35.