Use of Decitabine in Myelodysplastic Syndrome (MDS) Following Azacitidine (AZA) Failure (DEC-MDS)

END OF STUDY REPORT

1. Details of Chief Investigator

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2. Details of study

Full title of study:	Use of Decitabine in Myelodysplastic Syndrome (MDS) Following Azacitidine (AZA) Failure (DEC-MDS)
REC reference number:	10/H0808/76
Sponsors:	King's College Hospital NHS Foundation Trust and King's College London
EudraCT Number:	2009-017098-40
Number of Centres	5
Number of Patients	25 – Signed consent

3. Commencement and completion dates in the UK

First Patient First Visit	12 – Dec - 2010
Last Patient Last Visit	28 – Mar -2014

4. Primary Objective

To assess the overall response rate (CR+PR as per IWG 2006) at 6 months in MDS patients, CMML-2 patients, and AML patients with up to 30% bone marrow blasts (previously classified as RAEB-t by the FAB MDS classification), treated with low-dose decitabine who have previously failed therapy with 5-azacitidine.

5. Background and Rationale

Myelodysplastic Syndromes (MDS) are a relatively common group of myeloid neoplasms that occur predominantly in the elderly (the median age at diagnosis is 65 years). MDS has a median survival of 20 months and may progress to life-threatening failure of the bone marrow or develop into acute myeloid leukaemia (AML), which occurs in around 30% of patients. General symptoms associated with MDS include fatigue, dizziness, weakness, bruising and bleeding, frequent infections, and headaches. There are at least 2000 new diagnoses of MDS per year in the UK. (2015 people were newly diagnosed with MDS in England in 2006, and 919 registered deaths in England and Wales in 2005). Approximately half of the patients have International Prognostic Scoring System (IPSS) Int-2/high risk disease with a median survival of 0.4-1.2 years.

Allogeneic haematopoietic stem cell transplantation is the only proven curative therapy for MDS. However, in view of the advanced age and associated co-morbidities this is not an option for the majority of patients. More recently, DNA methyltransferase (DNMT) inhibitors have been shown to be a promising treatment option for MDS patients. Epigenetic alterations such as DNA methylation aberrations and abnormal histone post-translational modification patterns are widespread in cancers cells including MDS and leukaemia (Leone 2002). 5-azacitidine and decitabine are cytosine nucleotide analogues that are respectively either indirectly or directly incorporated into DNA, inhibiting further DNA methylation. It is postulated that as a results of this action, aberrantly silenced genes in MDS, such as tumour suppressor genes, are re-expressed.

Both 5-azacitidine and decitabine are approved by the FDA for the treatment of de novo and secondary MDS patients with intermediate-1, intermediate-2 and high-risk MDS, including the French-American-British (FAB) classification of refractory anemia with excess of blasts in transformation (RAEB-t) (20-30% bone marrow blasts) and chronic myelomonocytic leukaemia (CMML). 5-azacitidine prolongs the time to AML transformation and death (Fenaux 2009), with overall haematological response rates of 29% and haematological improvement rates of 49%. However, many patients will fail therapy with 5-azacitidine, either due to the inability to tolerate the agent, or due to disease resistance and relapse while on treatment. The outcomes of patients who fail treatment with 5-azacitidine is grim. As many of the patients who receive treatment with 5-azacitidine are elderly, have associated co-morbidities, or have poor risk disease, the therapeutic options are limited to supportive care only.

6. IMP - Decitabine

Several studies have shown the activity of decitabine in MDS. Wijermans et al has reported on the European experience of 177 patients with MDS (including RAEB-t and CMML patients) treated on multiple studies with decitabine (15 mg/m^2 IV over a 4 hour period, every 8 hours, for 3 days) (total dose 135-150 mg/m^2 per course) every 4-8 weeks. The overall response rate was 49%, with a CR rate of 20% which was higher than that observed in the 5-azacitidine studies. This was however offset by significant myelosuppression, with the induction mortality of this regimen noted at 8%.

Initial studies at MD Anderson Cancer Centre (MDACC), USA, investigated decitabine at the maximum tolerated dose (MTD) from the European studies. Decitabine was given at 50-100 mg/m^2 IV over 6 hours x 5 days (250-500 mg/m^2 per course). Objective response rates were 25-30% in CML blastic phase and 50-60% in accelerated phase. However, myelosuppression was delayed and prolonged. As a consequence, a phase I study was conducted in the same institution to determine the "optimal biologic dose" in patients with relapsed/refractory AML, high-risk MDS and chronic myeloid leukemia in blast crisis. The first cohort of patients received decitabine 5 mg/m^2 as a 1-hour infusion daily for 5 days/week, for 2 consecutive weeks. Doses were increased in increments of 5 mg/m^2 in

successive cohorts based on toxicity and response. The decitabine optimal schedule was judged to be 15 mg/m^2 IV over 1 hour daily x 10 days, and the overall response rate was 32%: AML 23%, CML 4/5, MDS 4/7.

Following the above experience, MDACC sought to optimize the dose scheduling of decitabine by investigating, in a randomized "play the winner design," 3 schedules of decitabine in MDS (total 100 mg/m^2/course in all 3 arms):

- Decitabine 10 mg/m^2 IV over 1 hour daily x 10
- Decitabine 20 mg/m^2 IV over 1 hour daily x 5
- Decitabine 10 mg/m^2 subcutaneously twice daily x 5

Patients had MDS as per FAB classification, de novo and secondary, and both pre-treated or treatment-naïve. Each treatment regimen was given every 4 weeks, Of the 95 randomized patients, CR rates were higher for those patients treated with 20 mg/m^2/day IV for 5 days (39%), than those treated with 10 mg/m^2 twice daily SC (21%) or 10 mg/m^2 daily IV for 10 days (24%). Severe Grade 3-4 drug related non-hematologic toxicity was uncommon and did not result in dose delay or reduction. Despite infectious complications, 32 of the 95 patients (34%) were never hospitalized. Of note, there was more myelosuppression and a higher incidence of hospitalization with the 10-day IV schedule. Overall, only 14% of patients and 14% of treatment courses required dose reduction.

Of note, the use of decitabine in a low-dose protocol of 20mg/m^2 intravenously daily for 5 days had a high complete response (CR) rate of 39%, in contrast to the CR rate of 7-10% from the CALGB 9221 studies using single agent 5-azacitidine. A prospective multicentre study evaluating the low –dose decitabine regimen in 99 MDS patients has recently confirmed an overall response rate of 32%, with 17 complete responses and 15 marrow CRs, and an overall improvement rate of 51% (Steensma 2009)
Decitabine was granted FDA approval in May 2006 for the treatment of intermediate-1, intermediate-2 and high-risk MDS, including patients with the FAB classification of RAEB-t (20-30% bone marrow blasts) and CMML. It was also granted Orphan Drug status by the EMEA in 2006; however it has yet to receive a Marketing Authorisation within Europe.

7. Inclusion Criteria

1. Written signed informed consent.
2. 18 years of age or older
3. At study entry, diagnosed MDS with 5% or more marrow blasts and IPSS risk intermediate 2 or high risk; or chronic myelomonocytic leukemia (CMML-2); or AML with 20-30% bone marrow blasts (previously defined as RAEB-t by the FAB MDS classification).
4. Patients who have failed therapy with azacitidine* see definition below.
5. Performance status 0-2 (ECOG scale).
6. Adequate hepatic (bilirubin < 1.5 X ULN or AST< 2.5 X ULN) and renal functions (creatinine <1.5 X ULN).

***Failure of treatment with 5-azacitidine is defined as:**

1. Refractory
   Progression, immediately and without reaching prior response (CR, PR, mCR, HI), under therapy with 5-azacitidine given for at least 6 cycles

2. Relapsed on therapy
   Progression, after prior response (CR, PR, mCR, HI, SD), under therapy with 5-azacitidine

3. Relapsed off therapy
   Patients who had previously attained a response (CR, PR, mCR, HI, SD) while on 5-azacitidine, but have subsequently relapsed within 3 months from last 5-azacitidine course

4. Toxicity failure
   5-azacitidine-related non-haematological toxicity precluding its further administration

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Disease Progression is defined as:	For patients with <5% blasts: a ≥50% increase in blasts to >5% blasts; For patients with 5% to 10% blasts: a ≥50% increase to >10% blasts; For patients with 10% to 20% blasts: a ≥50% increase to >20% blasts; One or more of the following: ≥50% decrement from maximum remission/response levels in granulocytes or platelets, reduction in hemoglobin concentration by ≥20 g/L or transfusion dependence.[4]

8. Exclusion Criteria

1. Patients with >30% bone marrow blasts at study entry.
2. Nursing and pregnant females.
3. Women of childbearing potential (WCBP) [†] and males not willing to practice an effective method of contraception whilst receiving decitabine and for 2 months after the last infusion.

   [†] A woman of child-bearing potential is a sexually mature woman who has not undergone a hysterectomy or bilateral oopherectomy or who has not been naturally postmenopausal for at least 24 consecutive months (i.e., who has had menses at any time in the preceding 24 consecutive months).
4. Patients with concurrent malignancy.
5. Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure and unstable angina pectoris.
6. Ongoing oral corticosteroids are not permitted. However, use of corticosteroids (topical and inhaled) is permitted and prophylactic steroids are allowed for transfusion reactions.
7. Patients who have received any investigational agent within the 30 days preceding the first dose of study drug.
8. Patients who have received prior intensive combination chemotherapy or high-dose cytarabine (>/= 1g/m*2 per dose) for the treatment of MDS or AML. (Prior biologic therapies, targeted therapies and single agent chemotherapy are allowed).
9. Patients who have an active viral or bacterial infection. Note: No patient is allowed to enter the study unless infections have been fully treated and the patient has remained afebrile for 7 days without antibiotics.
10. Patients who have concurrent autoimmune hemolytic anemia or immune thrombocytopenia.
11. Patients who have previously been treated with decitabine.
12. Patients who have known positive serology for HIV.
13. Patients with a condition that may be unable to comply with the treatment and monitoring requirements of the study.

Subjects cannot receive any chemotherapy or radiotherapy between the failure to 5-azacitidine and the start of study medication (decitabine).

Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

9. Treatment Plan

Time and events schedule							
Visit Day	Screening	Cycle 1-6 of study			Extension Phase[a]	End-of-treatment[b]	Follow-up[c]
	Within 4 weeks of treatment	Day 1 of each 28 Day Cycle	Every week[r]	End of 3rd and 6th cycle	Day 1 of each 28 Day Cycle	30 ± 2 days from last dose	Every 3 months
Informed Consent	X[g]						
Demographics (DOB, gender, origin)	X						
Medical/Treatment History	X						
Physical Assessment	X	X[i]			X[i]	X	
Vital Signs[d]	X	X[i]			X[i]	X[q]	
BSA	X	X[in]			X[in]		
Concomitant Medications	X	X			X	X	
Transfusion Requirements	X	X			X	X	
Pregnancy Test (Serum or Urine)[l]	X	X[i]			X[i]	X	
Haematology[o]	X	X[i]	X		X[i]	X	
Biochemistry[p]	X	X[i]	X		X[i]	X	
Bone Marrow Aspirate and Trephine (including cytogenetic analysis)[m]	X[h]			X[j]			
Blood sampling for exploratory analysis	X[h]			X[k]			
AE assessment[e]		X----------X				X	
Assessment for: Survival, Relapse, Subsequent treatment							X
Decitabine administration[f]		Day 1 to Day 5 of 28 day cycle					

a Extension Phase: Patients achieving clinical response (as defined as CR, PR, or haematological response, including HI and SD based on the IWG 2006 response criteria – Appendix D) after 6 cycles of decitabine will remain on treatment in the extension phase. Treatment will be continued as long as patients demonstrate evidence of clinical response.

b End of treatment visit: 30 days +/- 2 days after receiving last dose of study medication.

c Follow-up: Patients will be assessed every 3 months until 1 year after last dose of study medication.

d Vital signs to be recorded: height (only at baseline), weight, ECOG performance score.

e Adverse events must be captured from the start of the treatment period up to and including 28 days after the last dose of study medication.

f Decitabine will be administered as a 20mg/m^2 1-hour intravenous infusion once daily on Days 1 to 5 of a 4 week cycle. In case of an obese patient (Body Mass Index >/= 30 kg/m^2) the dosing should be calculated based on adjusted ideal body weight (AIBW). Treatment will be given on an outpatient basis.

g Informed consent must be obtained before any trial related tests or procedures unless taking place as part of routine standard practice.

h Informed consent must be obtained before bone marrow biopsy/aspirate and peripheral blood samples are collected for the exploratory analysis. Consent for these samples will be obtained using a separate consent form under the auspices of NRES protocol 08/H0906/94. If the bone marrow biopsy is performed within 4 weeks of treatment (within the screening period) but before informed consent has been obtained, it is not necessary to repeat the bone marrow biopsy/aspirate (or peripheral blood) for the purposes of exploratory analysis. Samples for exploratory analysis will be sent to the Research Tissue Bank at Kings College Hospital for banking. The procedure for dispatch of exploratory samples is detailed in Appendix E.

i To be taken before decitabine dosing.

j To be performed at the end (day 21+) of the 3rd cycle and 6th cycle. For cycles 3 and 6, collect additional bone marrow biopsy/aspirate (approximately 2 to 5 ml) for the exploratory analysis if exploratory samples obtained at screening.

k Blood sampling for exploratory analysis will be collected at the end (day 21+) of the 3^{rd} and 6^{th} course of decitabine treatment if exploratory samples obtained at screening.

l For women of childbearing potential only.

m BM assessment will be performed as set out in schedule and if there is clinical suspicion of disease refractoriness or relapse.

n BSA to be recalculated if weight changes by >10% (see section 3.2.)

o Obtain FBC with differential (absolute values) and platelets. Peripheral blasts should be assessed.

p Obtain serum chemistries, including urea, creatinine, potassium, sodium, corrected calcium, total bilirubin, AST, and alkaline phosphatase.

q ECOG performance score only.

r Day 8, 15 and 22 (+/- 2 days)

10. Study Results

The protocol (V7.1 31/07/2013) indicated an interim analysis which incorporated an early stopping rule. *'The trial needs to observe at least 2 overall responses out of 21 patients within 6months in order to proceed to the next stage where a further 20 patients will be recruited'.*

In light of this, an agreement was reached by members of the trial steering committee (TSC) that due to recruitment targets not being met and lack of efficacy being shown in the subjects that were recruited the trial should close to both recruitment and further activity.

At the time the trial was terminated (MHRA notification 02/Sept/2014), a total of 25 patients across all sites had consented onto the study. Only 20 patients actually received 1 or more cycles of Decitabine. Only 5 patients had 6 cycles or more and no patients met primary end point (CR or PR as per IWG 2006).

At the interim analysis, a review of the current subjects recruited up to that point took place, as was the rate of recruitment. Based on this primary information it was decided by the TSC to close the study.

11. Safety Evaluation

The following SAEs (please see table below) were experienced by the study patients; there were no unexpected SAEs related to trial medication nor were than any significant AEs to report.

System Organ Classification	Date Of Onset	Serious Adverse Event/Reaction Details	Relationship to IMP	Recognised Adverse Reaction
Cardiovascular	14/05/2012	Suspected Heart abnormality	Possible	Yes
General disorders and administration site conditions	06/11/12 25/03/13 20/01/13 13/03/13 02/12/12 01/12/12 24/10/13	Pyrexia	Possibly related	Yes
Blood and Lymphatic disorders	15/08/13	GI bleed	Possibly	Yes
Infections and infestations	12/04/12 17/04/12 09/11/2012 02/01/13 28/01/13 16/02/13 19/02/13 14/03/13 04/04/13 27/07/13	Neutropenic Sepsis	Possibly related	Yes
	18/01/2011	Sepsis	Possible	Yes
	17/04/12	Infection	Possible	Yes

System Organ Classification	Date Of Onset	Serious Adverse Event/Reaction Details	Relationship to IMP	Recognised Adverse Reaction
Respiratory	30/01/13	Apergillosis	Not related	No
	09/09/11	Pneumonia - Grade 3	Not related	No
	05/12/2011	Oedema & shortness of breath.	Not related	No
General disorders and administration site conditions	30/07/12 24/08/13	Pyrexia	Not related	No
Infections and infestations	21/04/2011 07/02/12	Neutropenic sepsis	Not related	No
	06/10/13	Sepsis	Unlikely	No
	30/08/13	Infection	Not related	No
	23/10/13	Bacterial Infection	Unlikey	No
Blood and Lymphatic disorders.	24/04/13	Mild Epitaxis	Not related	No
	07/10/13	GI Bleed	Unlikely	No
	10/05/2012	Extramedullary Haemopoiesis	Not related	No

12. Declaration

Signature of Chief Investigator:	
Print name:	Professor Ghulam J. Mufti
Date of signature:	19th June 2015