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HIGH RISK MDS AND HYPOMETHYLATING AGENTS



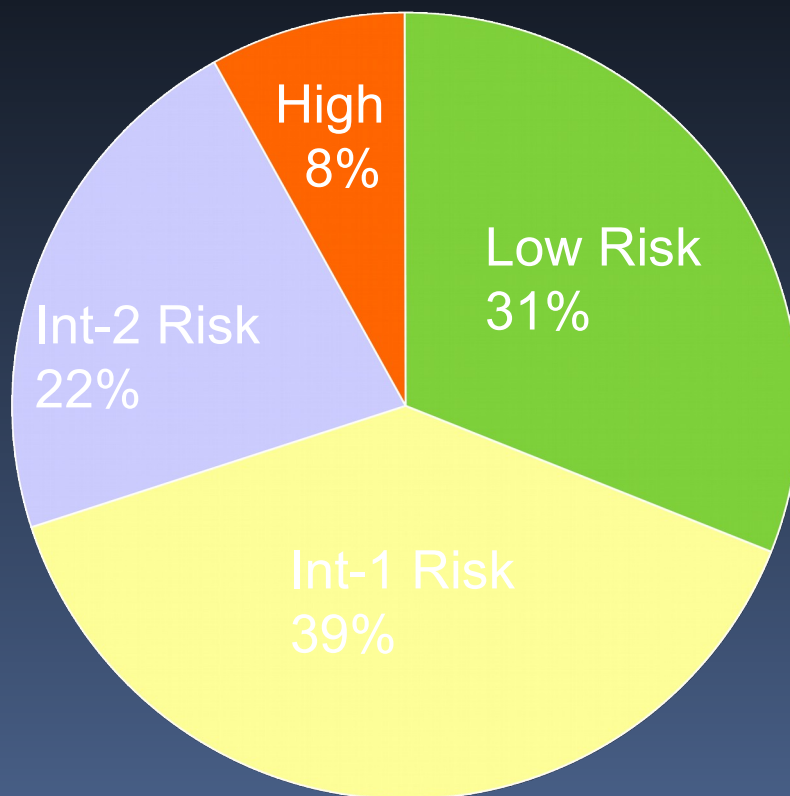
IPSS scoring system

- Blood counts
 - Bone marrow blast percentage
 - Cytogenetics
- 

Age as a modulator of median survival


IPSS Group	Median Survival (years)	Age \leq 60 years	Age >60 years	Age >70
Low	5.7	11.8	4.8	3.9
Intermediate-1	3.5	5.2	2.7	2.4
Intermediate-2	1.2	1.8	1.1	1.2
High	0.4	0.3	0.5	0.4

IPSS Risk Categories Distribution




*Estimated survival and risk of AML transformation

Greenberg PL et al. *Blood*. 1997;89:2079




Goals for treatment

- Individual
 - Prolong overall survival with best quality
 - Prevent disease progression
 - Achieve Complete remission
 - Minimal side effects of therapy
- 




Treatment Options

- Best Supportive care
 - Low dose chemotherapy
 - Intensive chemotherapy
 - Haemopoietic stem cell transplantation
 - Hypomethylating agents
- 




Best Supportive Care

- Blood and platelet transfusions
 - GCSF
 - Prophylaxis against infection if prolonged neutropenia
 - Iron chelation therapy
 - No longer the mainstay of MDS therapy
- 




Low Dose chemotherapy

- Low dose cytarabine, subcutaneously
 - 20mg/m² daily for 10-14 days
 - Disease control
- 




Intensive chemotherapy

- Hospital admission for approximately 4 weeks
 - Combination of 2-3 drugs with cytarabine
 - Risk of infection
 - Risk of delayed recovery of blood counts, marrow aplasia
 - Achieve Complete remission (cytogenetic)
 - Likelihood of relapse unless consolidated with a stem cell transplant
- 



Haemopoietic stem cell transplantation

- Consolidative procedure after achieving complete remission can cure upto 40% of patients with MDS
 - Donor availability
 - Reduced intensity conditioned regimes have reduced toxicity
 - Infection
 - Immune side effects
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Hypomethylating agents

- Azacytidine
- Decitabine (deoxy analog of azacytidine)
- Act by inhibiting DNA methyl transferase
- Also called Methyl transferase inhibitors

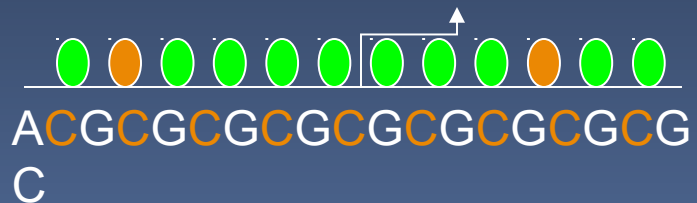
Promoter methylation of a gene



CpG Island with all 'C'
unmethylated ON

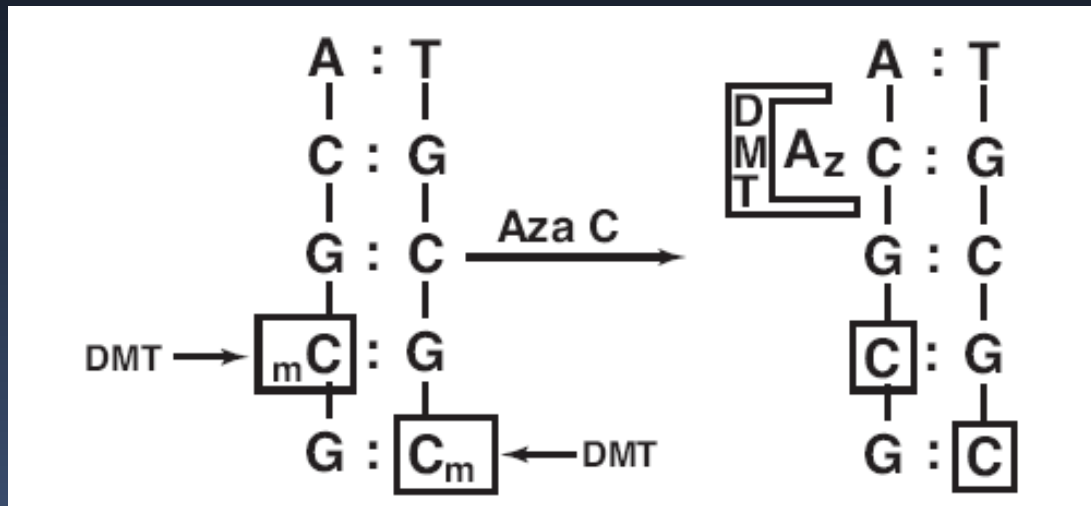


CpG Island with all 'C'
methylated OFF



Targeted Methylation
?effect on the gene

Mechanism of action

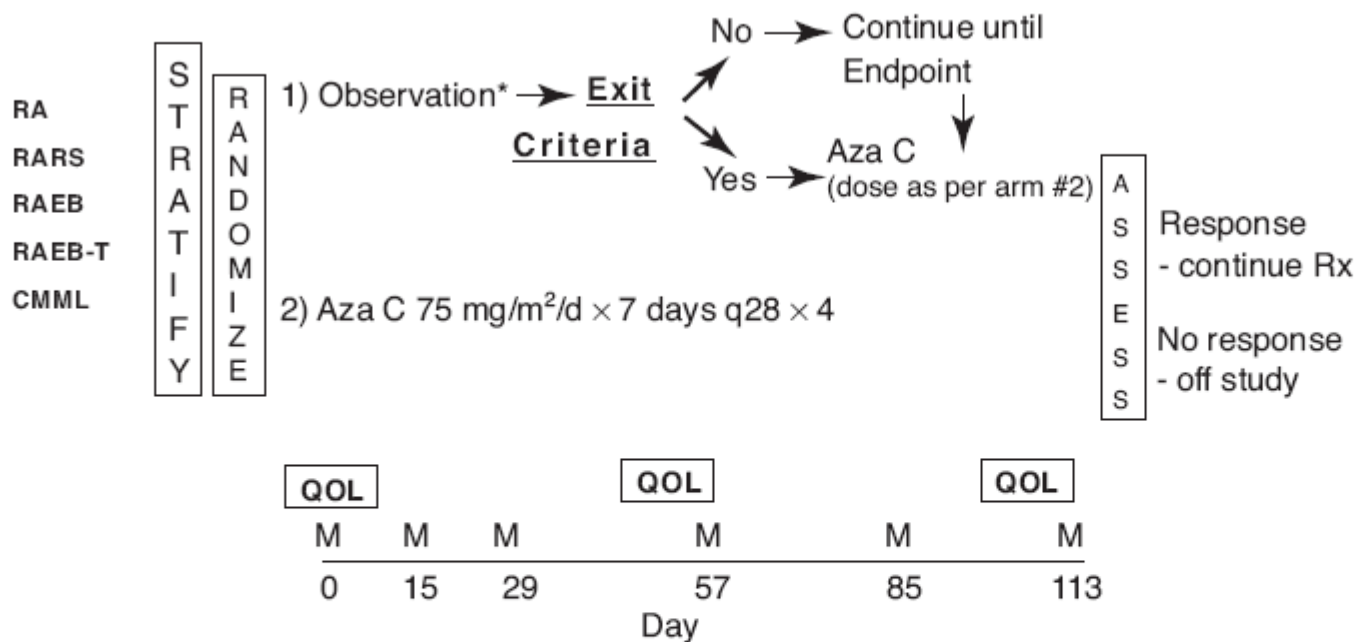


Silverman, 2001

Trials with Azacytidine

- CALGB 8221 and 8421, Phase II studies established median 4 cycles of treatment needed for a response and subcutaneous use
- CALGB 9221, Phase III randomised control trial compared Azacytidine with Best supportive care
Silverman et al JCO 2002
- AZA 001, Phase III randomised control trial comparing Azacytidine with Best supportive care, LD cytarabine or Intensive therapy Fenaux et al Lancet Oncology 2009

CALGB 9221



*Minimum duration of observation = 2 months

QOL = Quality-of-life assessment

M = Bone marrow

Aza C = azacytidine S.C.

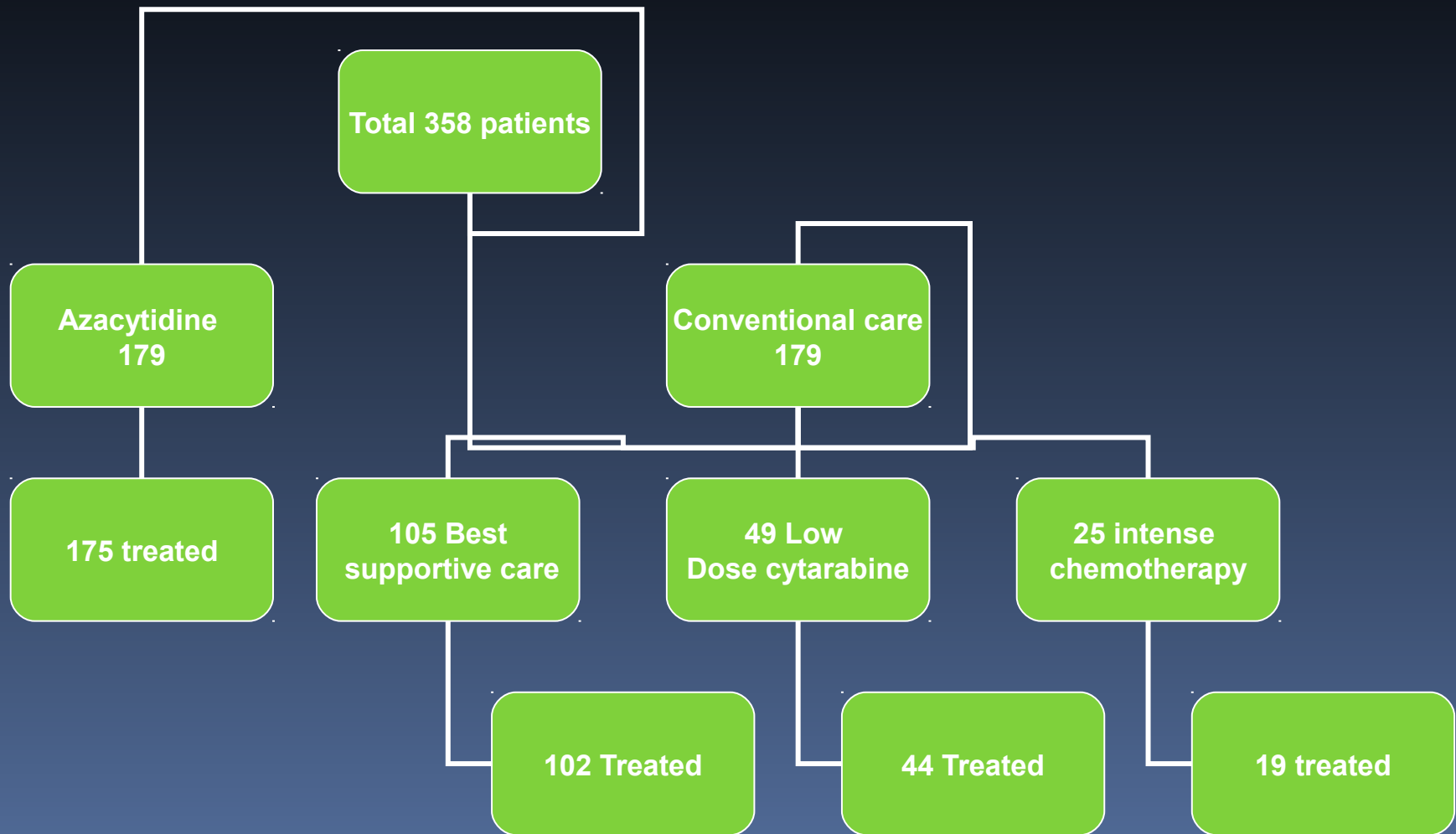
CALGB 9221 Results

- Azacytidine (99)
- Complete remission 7%
- Partial remission 16%
- Haematological improvement 37%
- Delayed time to AML by 9 months (12 vs 21 months)
- Best Supportive Care (92)
- Haematological Improvement 5%
- Overall survival 11 months

AZA 001


- Multicentre, international
- High risk MDS
- IPSS Int-2 or high
- FAB RAEB RAEB-t or CMML (<10% blasts
- Previously untreated
- Treatment option predetermined by physician

Aza 001 Trial design



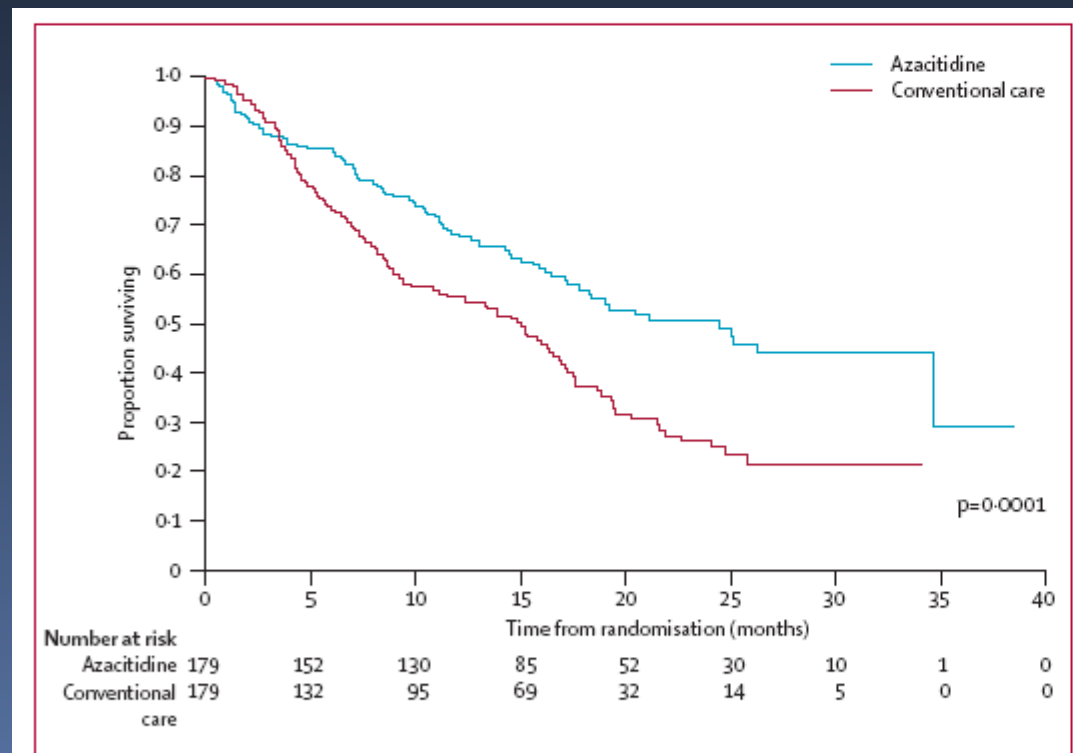


Results

- Median Age 69 years, 72% >65 years
 - Survival at 2 years was doubled for patients treated with Azacytidine versus conventional care (50.8% vs 26.2%, $p < 0.0001$)
 - Time to leukaemia transformation was 17.8 months for azacytidine group versus 11.5 months in the conventional care ($p < 0.0001$)
- 


Overall survival

- Overall survival for Azacitidine 24.5 months vs 15 months with conventional care ($p=0.0001$)





Results


- Azacytidine was superior
 - To BSC
 - Low dose chemotherapy
 - As effective as intensive chemotherapy
- 

Azacitidine for patients with 7q-/del17q

- Azacytidine prolonged survival to 19.8 months
- AZA001 30 Azacitidine 27 CCR
- Overall survival 13.1 vs 4.6 months
- 33% survived to 2 years
- Standard of care for this subgroup





Administration of Azacytidine

- 75mg/m² x7 days every 28 days
 - Subcutaneously
 - Average sized person two injections daily
 - Rotating sites, abdomen, thighs, upper arms
- 




Side effects of Azacytidine

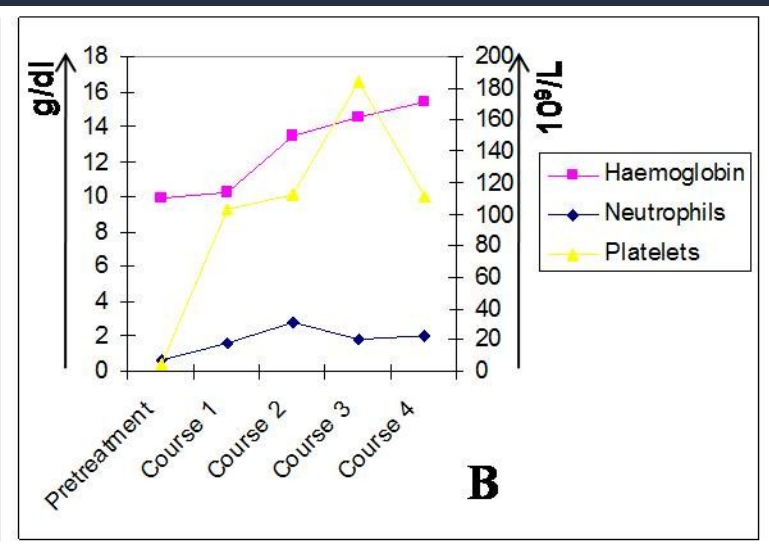
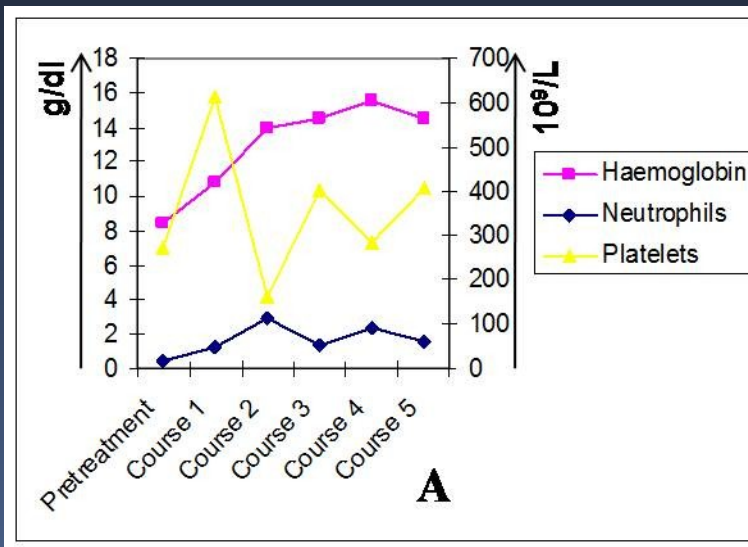
- Well tolerated
 - Increased blood or platelet requirements in the initial cycles
 - Nausea
 - Constipation/diarrhoea
 - Injection site reaction
 - Local nodules/bruises
 - Febrile neutropenia/sepsis
- 



Concomitant medications


- Antisickness medications
 - Topical cream for local reactions
 - Laxatives to counter constipation
 - Allopurinol to prevent gout
- 

Results





Decitabine


- Analog of Azacitidine
 - Phase III study
 - 45mg/m²/day x3 days q6 weeks IV
 - Decitabine n=89, BSC n=81
 - 43/89 received less than 2 cycles of decitabine
 - CR9%, PR8% HI13%
- 

Low dose decitabine

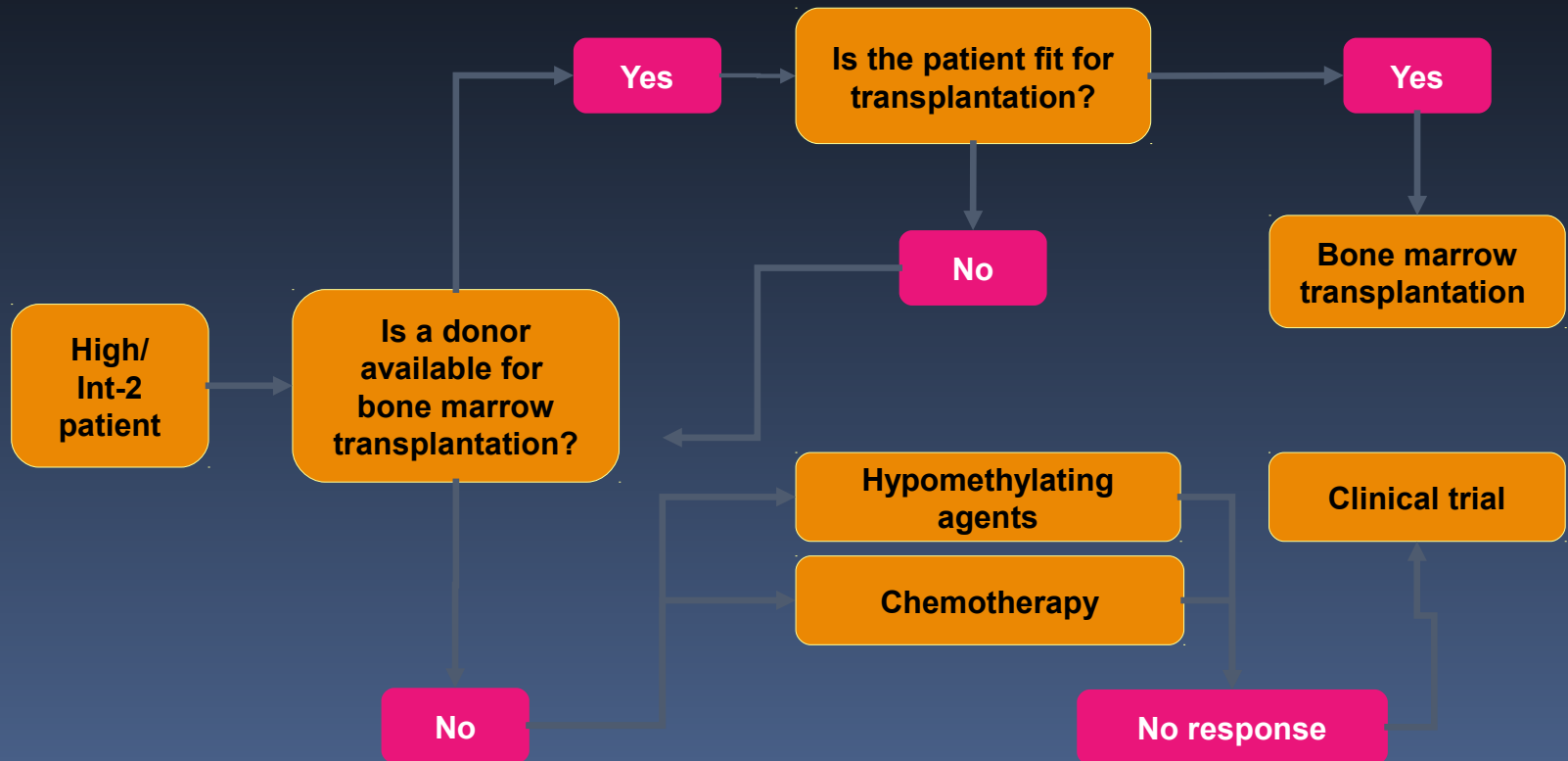
- IPSS 1.0, CMML, Phase I/II study
- 5-20mg/m²/day for 5/28 days IV
- Dose intensive schedule
- Unlimited cycles of therapy
- CR 34%, PR 1%, Marrow CR 24%, 13% HI
- 20mg/m²/day best responses CR 39%
- Median survival 19 months
- CMML 19 patients, CR 58%, HI 11%



Combination therapy

- Azacytidine with HDAC inhibitors
 - Vorinostat
 - Responses in approximately 80%
- 

Algorithm for treating high risk MDS






Summary

- MTI's should be considered for
- High risk MDS
- Particular patients with high risk cytogenetics
- Studies on improving outcomes with these drugs either alone or in combination are ongoing




Licensing of Azacitidine

- Licensed by the FDA for all subclasses of MDS
 - Azacytidine licensed by the EMEA for
 - Int-2
 - High risk MDS
 - CMML
 - AML with 20-30% blasts
- 



Access to drugs

- Trials NCRN AML 16, CMML
 - London cancer new drugs process of approval on going
 - NICE review QALY's too high, company resubmitting
 - ETA from local PCT
- 




Acknowledgement

- MRC
 - Prof Mufti
 - Dr Shaun Thomas
 - Patients at KCH and GSTT
- 






Current trials

- MTI prior to stem cell transplant
 - MTI maintenance therapy after AML induction therapy
 - MTI maintenance therapy after allograft
 - Alternative dosing strategies? Lower doses, 5 days a week?
- 




Primary Endpoints

- Primary endpoint overall survival
 - Survival by FAB subgroup
 - IPSS risk group
 - Cytopenia
 - Cytogenetics
 - -7/del(7q)
 - WHO classification
 - Serum LDH
- 



Treatment Schedule


- 75mg/m² sc 7/28 days for a minimum of 6 cycles
 - LD cytarabine 20mg/m² sc for 14 days/28 days for at least 4 cycles
 - Induction chemotherapy with Cytarabine/ Daunorubicine, idarubicine or mitoxantrone
 - If CR or PR one or two consolidation courses
 - Follow up 12 months after last patient enrolled
- 

WPSS risk groups and survival

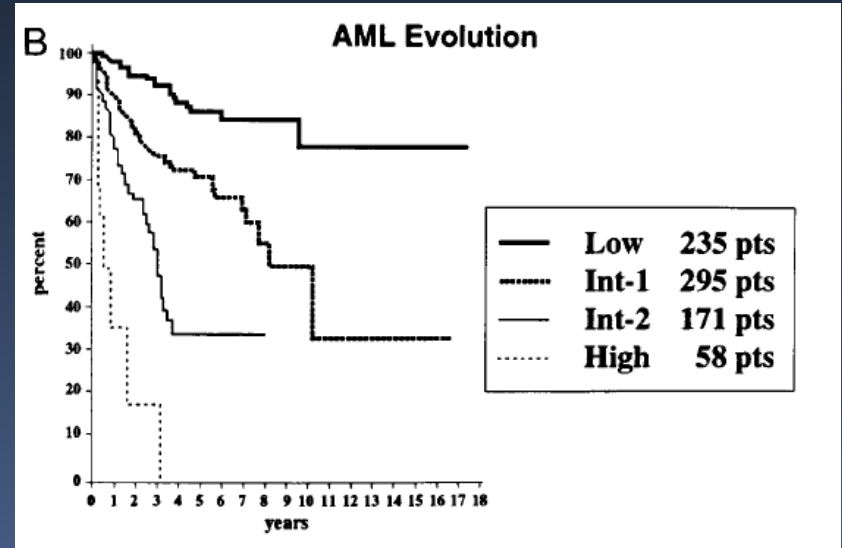
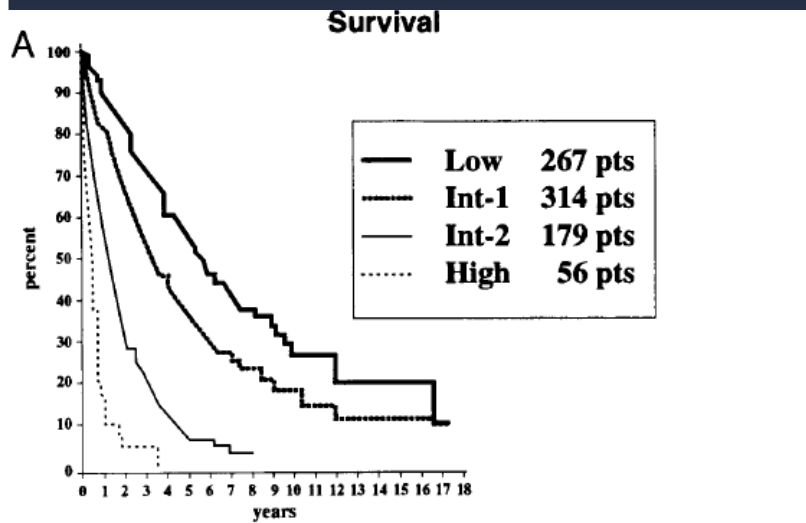
WPSS Risk Score	WPSS Risk Group	Median overall Survival months	Cumulative probability of leukaemic transformation at 2 years
0	Very Low	141	0.03
1	Low	66	0.06
2	Intermediate	48	0.21
3 or 4	High	26	0.38
5	Very High	9	0.80



Epigenetics

- Chemical modifications of genes that affect their expression reversibly without alterations in their DNA sequence
 - Enable dynamic control of genes in a context driven manner ie in time and space
 - DNA methylation
 - Histone acetylation
- 

Survival and leukaemic transformation based on IPSS




HCT comorbidity score and transplant outcomes

Sorrer et al JCO 2007

Risk Group	Type of conditioning	Non Relapse Mortality (%)	Relapse(%)	Overall Survival (%)	Relapse free survival (%)
Group 1 HCT-CI score 0-2, low risk disease	MA (n=138)	11	14	78	75
Group 2 HCT-CI score 0-2 and intermediate or high risk disease	NMA (n=28)	4	22	70	63
	MA (n=176)	24	34	51	43
	NMA (n=34)	3	42	57	56
Group 3 HCT-CI score 3 and low risk disease	MA (n=52)	32	27	45	41
	NMA (n=19)	27	37	41	36
Group 4 HCT-CI score 3 and intermediate or high risk disease	MA (n=86)	46	34	24	20
	NMA (n=44)	29	49	29	23



Secondary End points

- Time to transform to AML
 - Haematological Improvement
 - Red cell transfusion independence
- 

Azacitidine vs best supportive care

	Azacitidine	BSC	HR	P value
Overall survival (months)	21.1	11.5	0.58	0.0045
Time to transformation to AML	15.0	10.1	0.41	<0.0001

Azacitidine vs Low dose cytarabine

	Azacitidine	LD cytarabine	HR	P value
Overall survival (months)	24.5	15.3	0.36	0.0006
Time to transformation to AML (months)	15.0	14.5	0.55	0.097

Azacitidine vs Intensive chemotherapy

	Azacitidine	Intensive Chemotherapy	HR	P value
Overall survival (months)	25.1	15.7	0.76	0.51
Time to transformation to AML (months)	23.1	10.7	0.48	0.19

Timing of transplantation

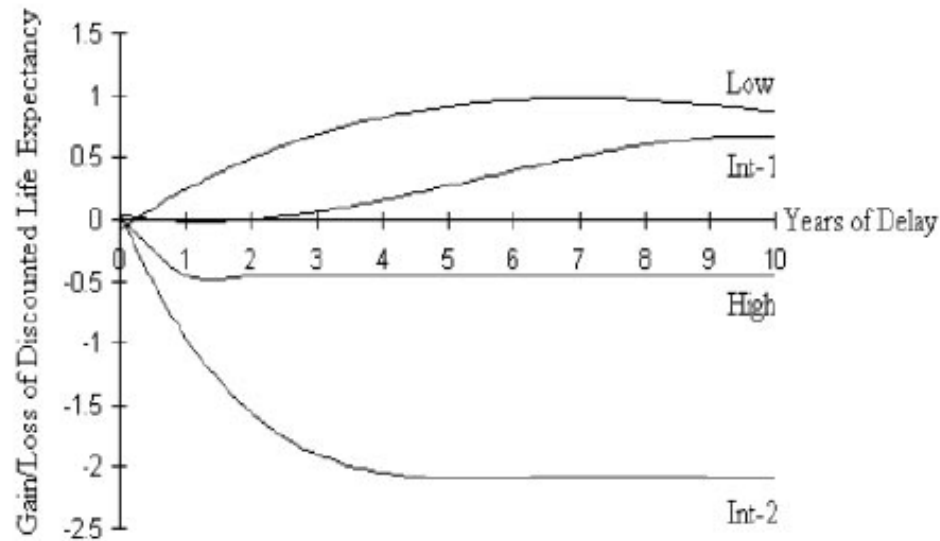


Figure 3. Net benefit or loss of overall discounted life expectancy for the 4 IPSS risk groups are shown above and below the x-axis. A net benefit for delaying transplantation is noted for low and int-1 risk groups, whereas any delay in the time to transplantation is associated with a loss in survivorship in the higher risk groups.

Myeloablative transplants

Delayed for low and int-1 MDS net gain of life expectancy

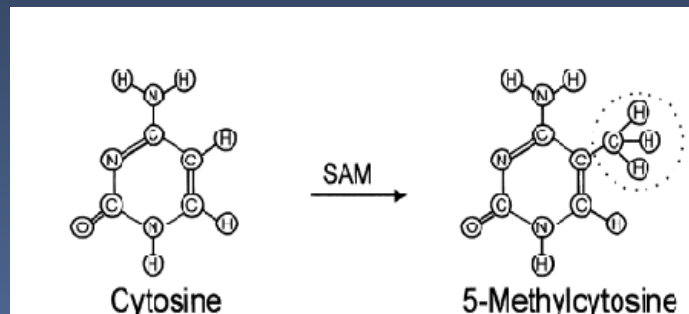
At diagnosis for Int-2 and High risk MDS is beneficial

DNA methylation

- 4 bases A,T,G,C.
- 5th base 5 methylcytosine
methyl from a s-adenosyl methionine is incorporated into position 5 of the cytosine ring.
- This is restricted to CpG dinucleotides
(cytosines that precede guanosine in the DNA sequence)

How does DNA become Methylated?

- * Enzymes called DNA methyltransferases (DNMTs) covalently link a methyl group from S Adenosyl Methionine to the 5 position of cytidine residues.

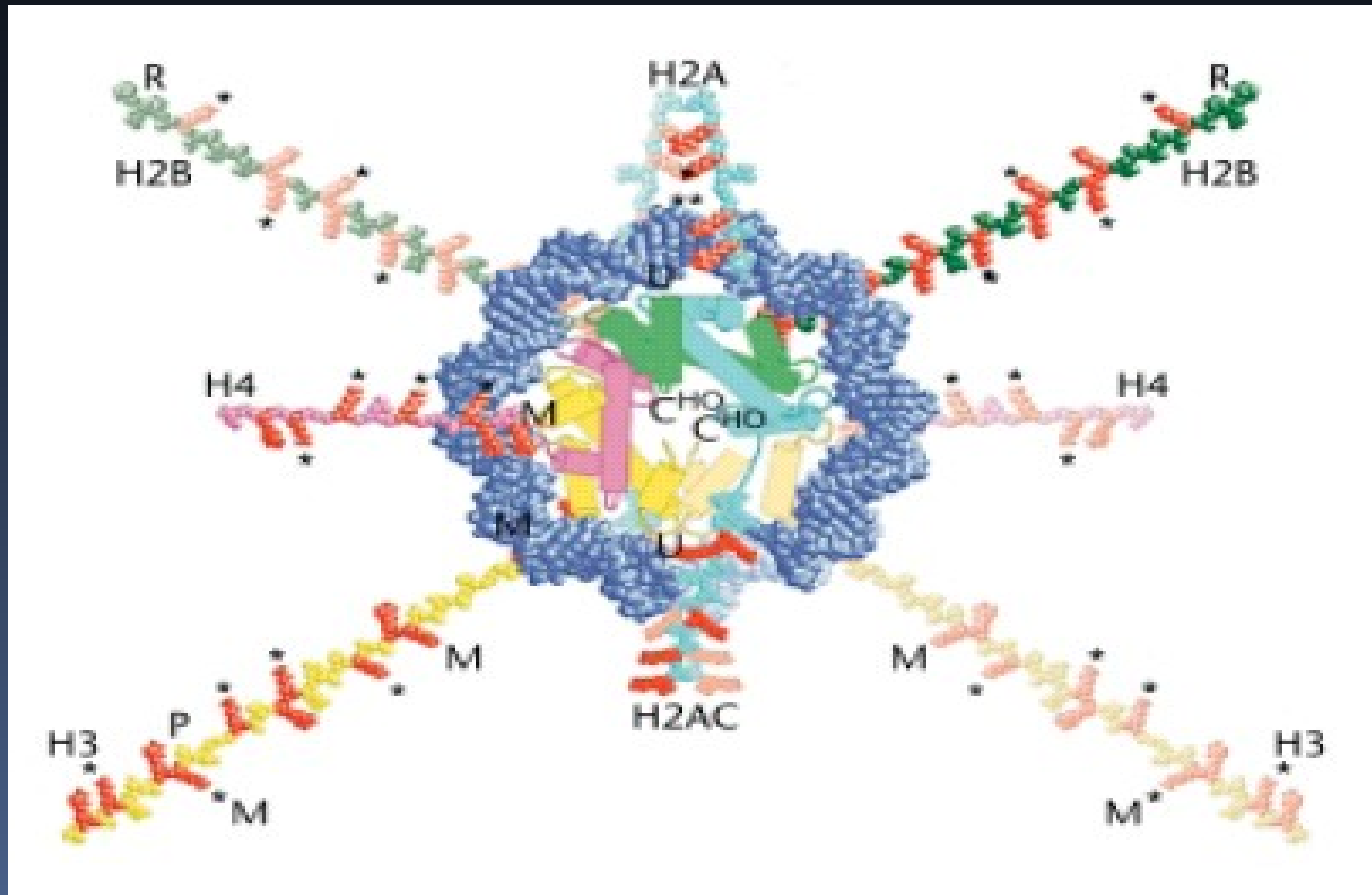


WHO Prognostic Scoring System

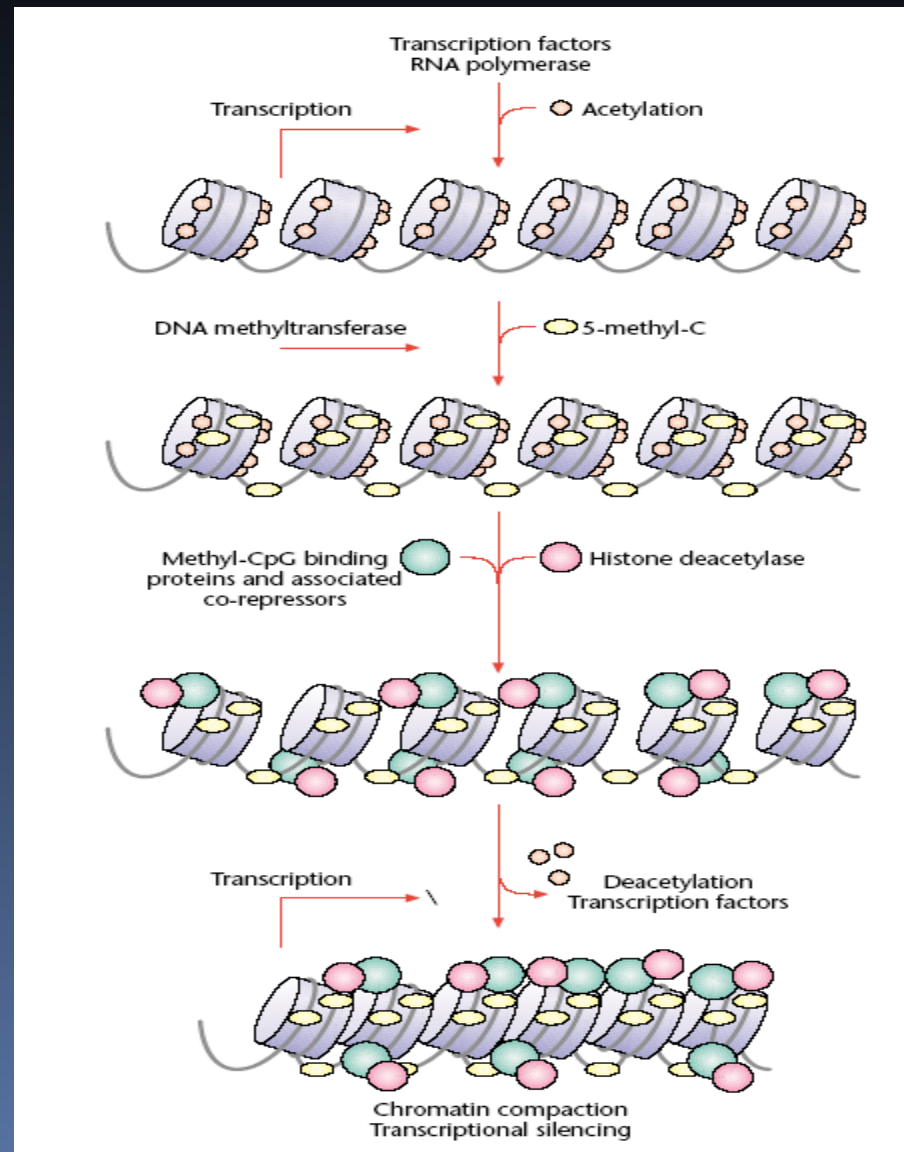
Variable	0	1	2	3
WHO Category	RA, RARS, 5q-	RCMD, RCMD-RS	RAEB-1	RAEB-2
Cytogenetics*	Good	Intermediate	Poor	
Transfusion requirement	No	Regular		

•*As per the IPSS subgroups

Histone Octamer



Silencing of a hypermethylated promoter



DNA methylation in MDS

- In cancer methylation of genes increases
- These are reversibly switched off
- Critical pathways such as cell cycle control, cell death, cellular growth, DNA repair may be affected
- In MDS: p15INK4b, MLH1, ER, may be silenced by methylation and may be critical to disease progression
- Responses to MTI have been linked with demethylation of genes

Haematological Response

Haematological response	Azacitidine	CCR	P value
Any remission	29%	12%	0.0001
Complete remission	17%	8%	0.015
Partial remission	12%	4%	0.0094
Stable disease	42%	36%	0.33
Haematological improvement			
Any	49%	29%	<0.0001
Major erythroid improvement	40%	11%	<0.0001
Major platelet improvement	33%	14%	0.0003
Major neutrophil	19%	18%	0.87




Acknowledgement

- MRC
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 - Dr Shaun Thomas
 - Patients at KCH and GSTT
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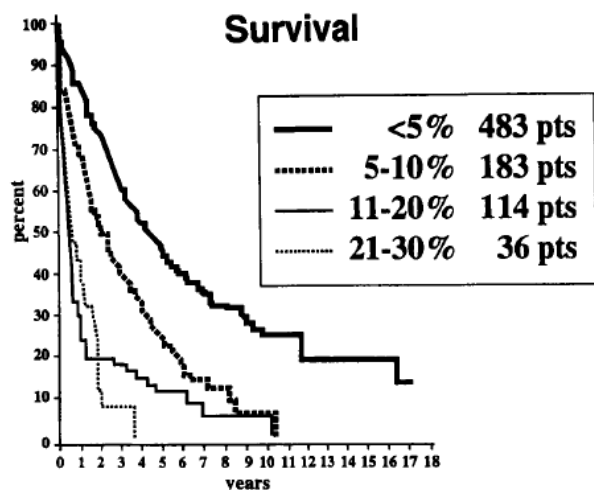


Disease Factors

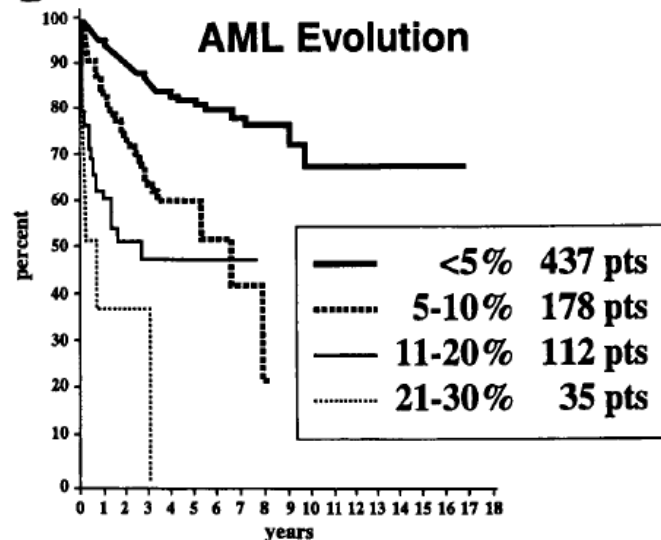
- Blast percentage
 - Cytogenetics: chromosome 7
 - Tempo of disease
 - De-novo or secondary MDS
- 

Blast percentage

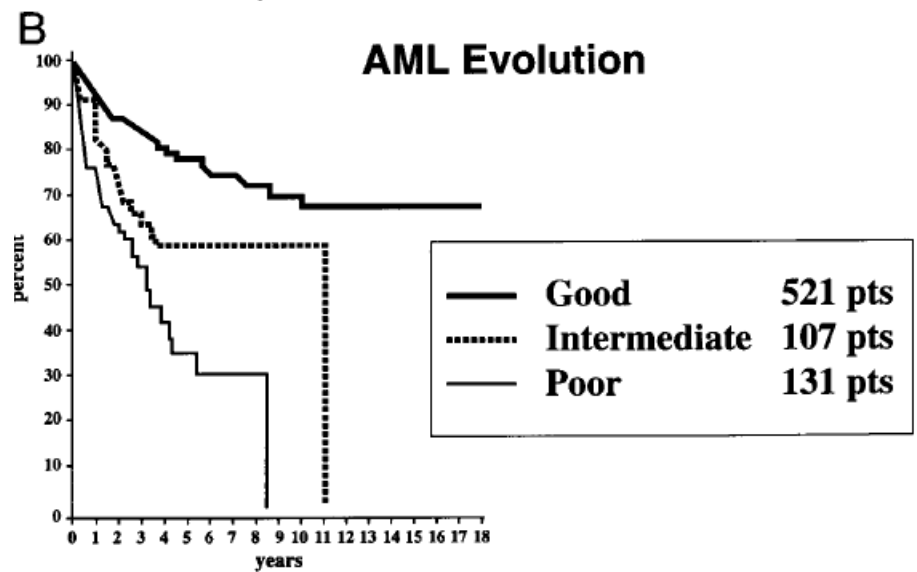
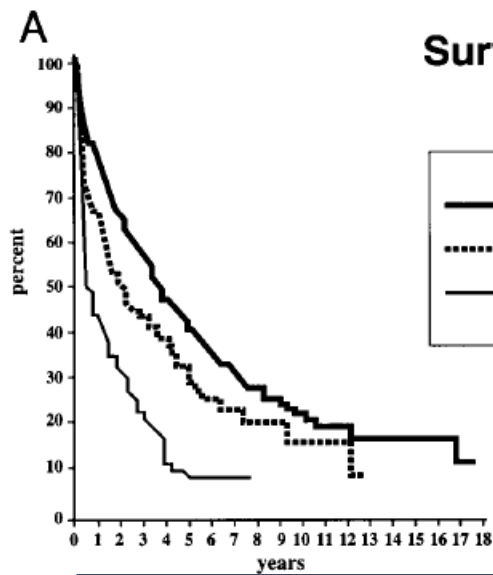
A Marrow Blasts



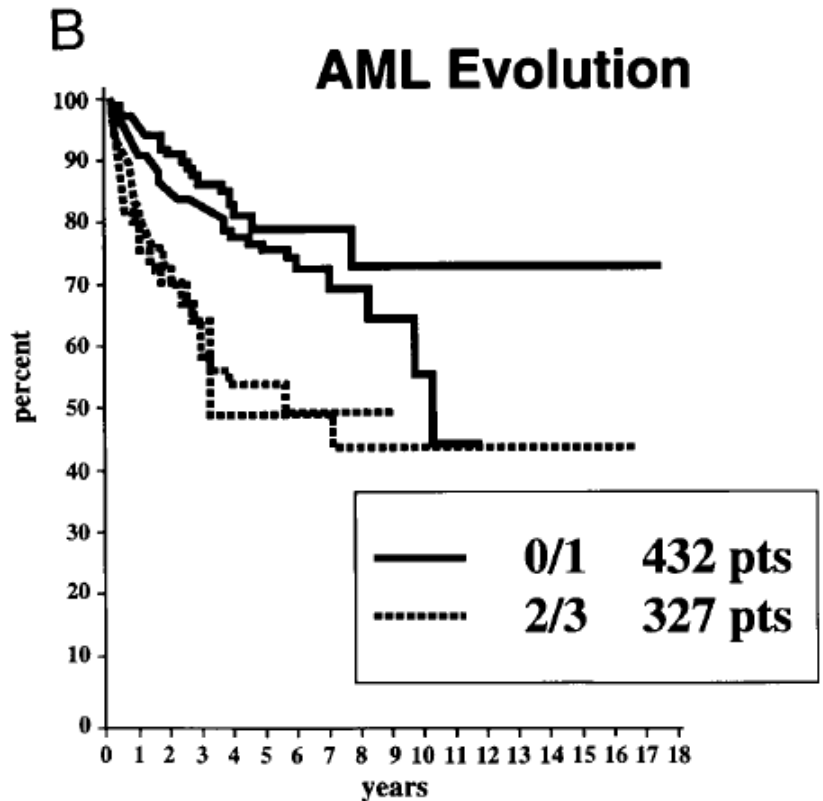
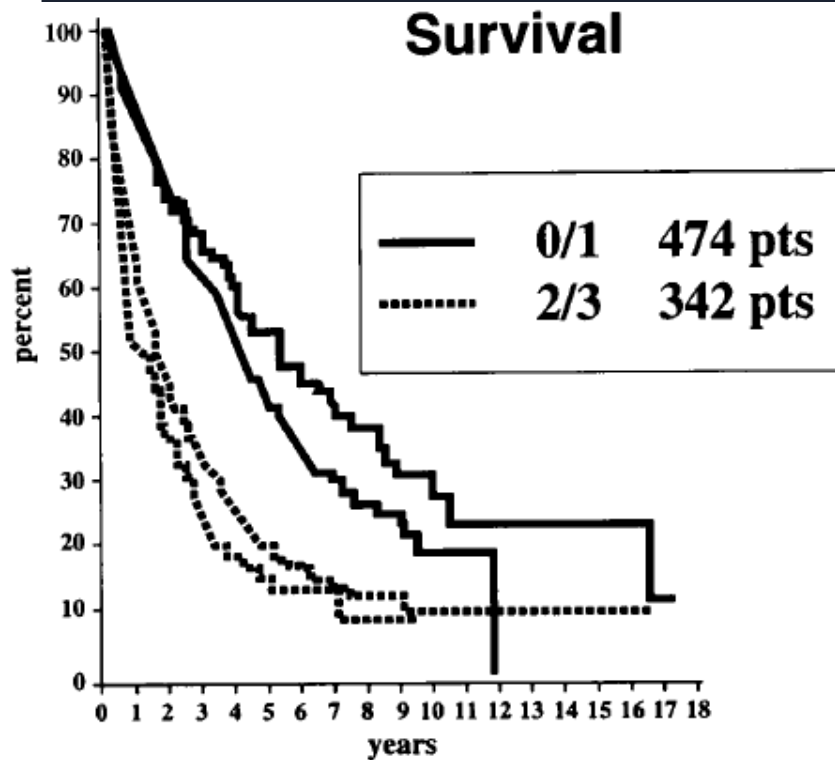
B AML Evolution

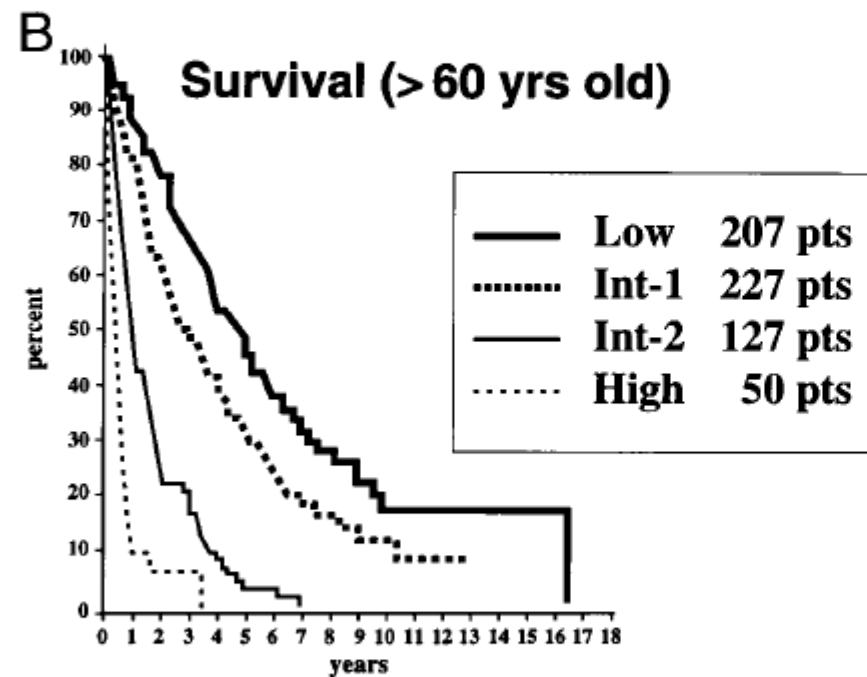
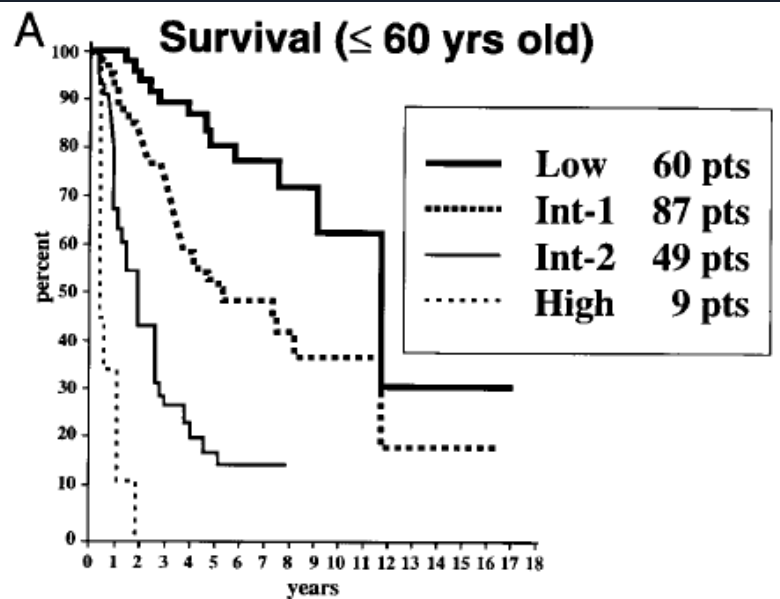


Cytogenetics




Cytopenia





Age as a modulator of leukaemic transformation

IPSS Group	Median time for 25% Risk of Leukaemia (years)	Age \leq 60 years	Age >60 years	Age >70 years
Low	9.4	>9.4 (not reached)	>9.4 (not reached)	>5.8 (not reached)
Intermediate-1	3.3	6.9	2.7	2.2
Intermediate-2	1.1	0.7	1.3	1.4
High	0.2	0.2	0.2	0.4



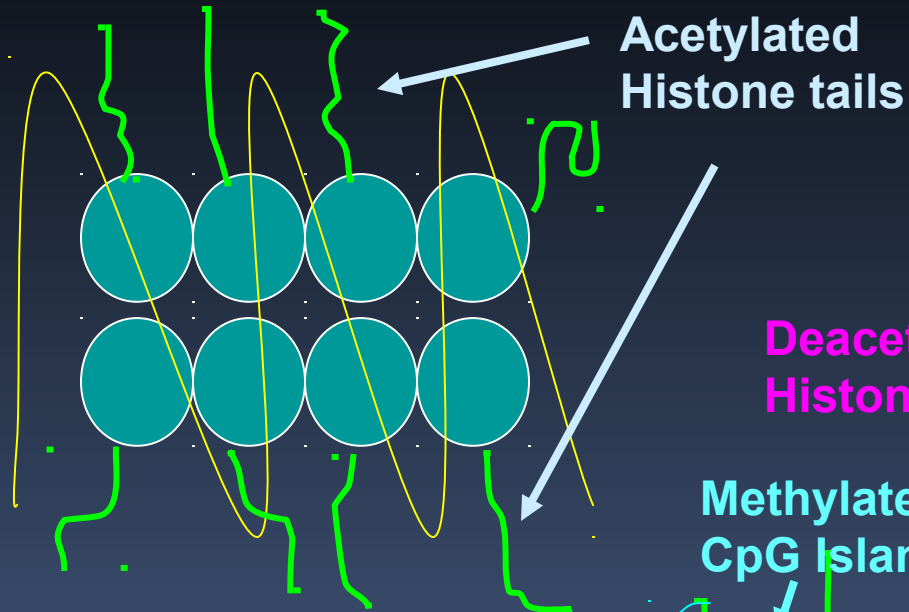
Choice of treatment

- Co-existing conditions
 - Cardiac: previous MI, prosthetic valves
 - Liver dysfunction
 - Pulmonary: COPD,
 - Mobility
 - Rheumatoid arthritis
 - High ferritin levels
- 

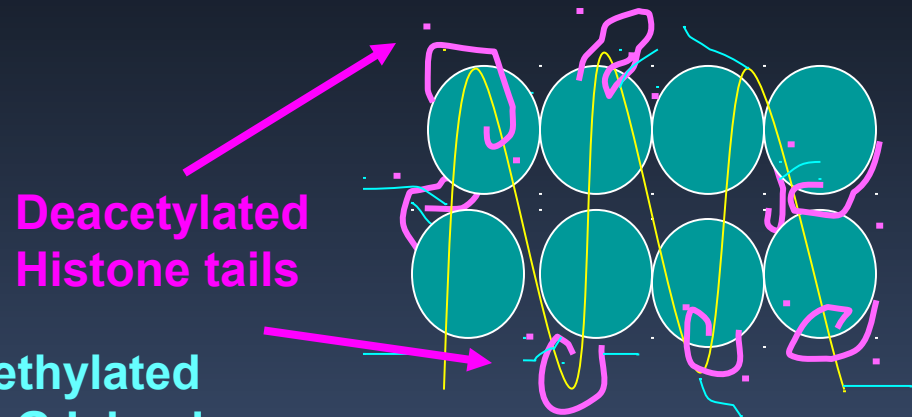
Cytogenetic Risk

- Good Risk
 - Normal
 - -Y only
 - del5(q) only
 - del 20q only
- Intermediate Risk: Other anomalies
- Poor Risk
 - Complex (3 or more abnormalities)
 - chromosome 7 abnormalities

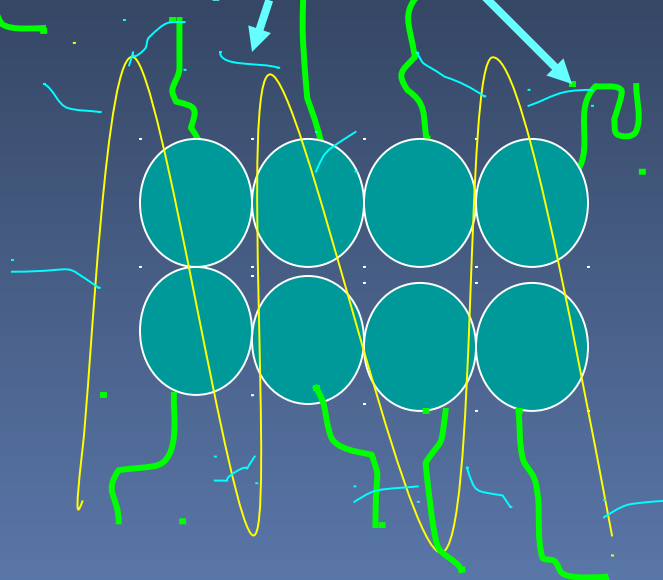
**Open Chromatin/
Transcriptionally
Active**



**Condensed Chromatin/
Transcriptionally Inactive**



**Methylated
CpG Islands**



**DNA
Methyltransferase**



MeCP2/Sin3/HDAC



IPSS Variables

Prognostic Variable	Score				
	0	0.5	1.0	1.5	2.0
BM Blasts	<5%	5-10%	-	11-20%	21-30%
Cytogenetics	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Score 0 Low Risk

0.5-1.0 Intermediate 1 risk

1.5-2.0 Intermediate 2 risk

≥ 2.5 High risk