Is there a role for autologous stem cell transplantation in the treatment of acute myelogenous leukaemia?

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Therapy of AML

- Induction Therapy
  - Combination chemotherapy
  - Cytarabine
    - High, low, Intermediate…
  - Daunorubicin
    - Thioguanine
    - Etoposide
- Optimal treatment schedule unknown
  - 5+1
  - 7+3
  - 10+ 3
  - TAD-HAM
  - Hi D-Arac
    - FLAG (+ida)
- Optimal post-remission management unclear
  - Standard 7+3
  - High dose Cytarabine (2-4 courses)
  - Autologous stem cell transplant
  - Allogeneic stem cell transplant
    - Need stem cell donor

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(* Eldestein et al, 1973, # Rai et al, 1981, Rees et al, 1986, @Preisler et al, 1987, Bishop 1990; Cassileth et al. N Engl J Med. 1998)

Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial

*Alan K Burnett, Anthony H Goldstone, Richard M F Stevens, Ian M Hann, John K H Rees, Richard G Gray, Keith Wheatley, for the UK Medical Research Council Adult and Children's Leukaemia Working Parties**

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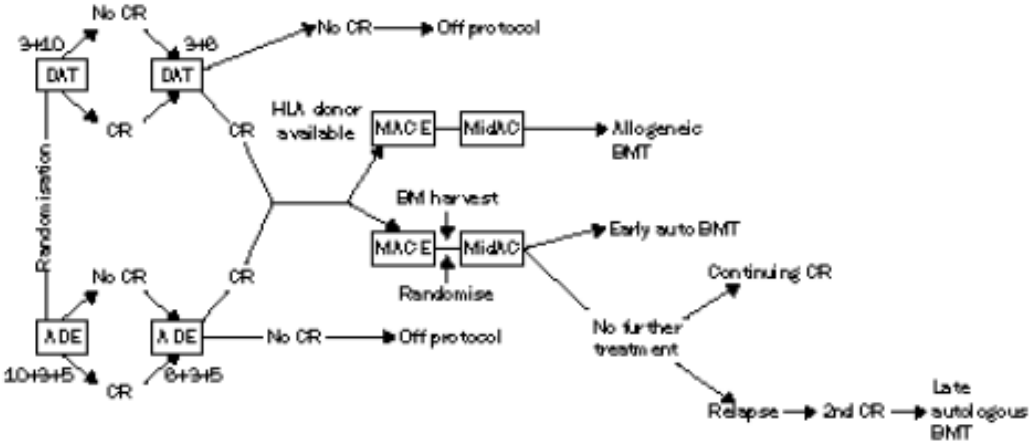

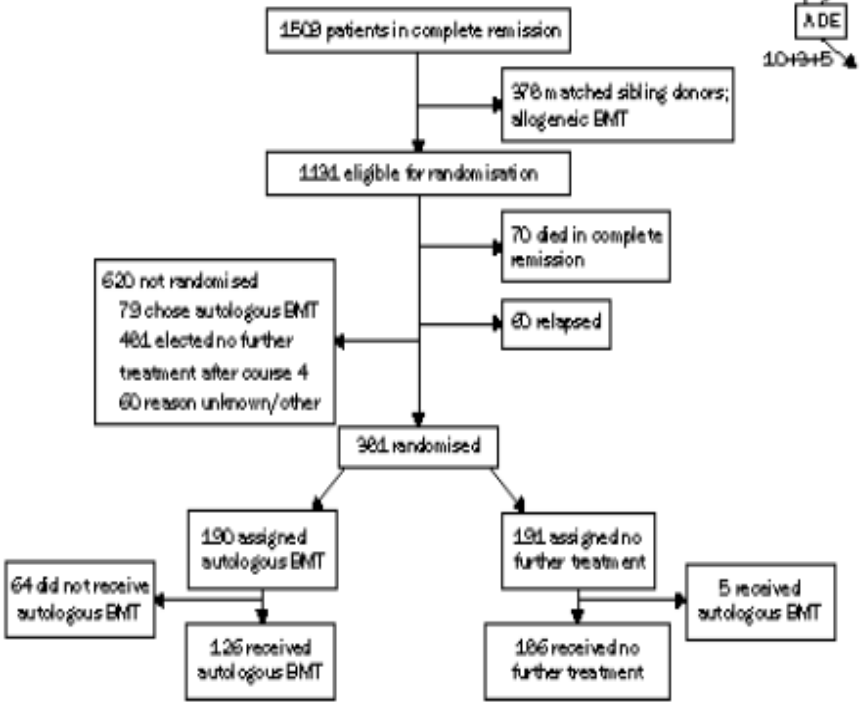

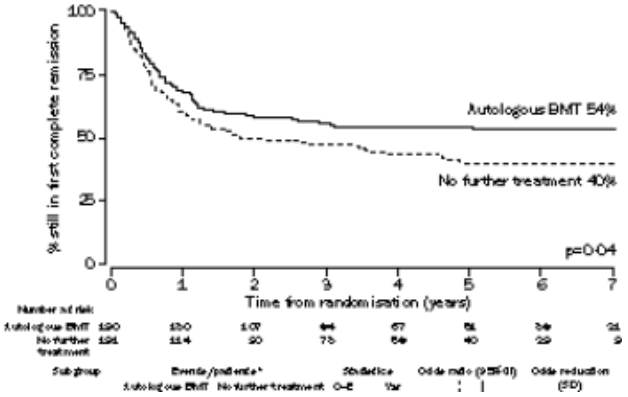

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Treatment Schedule

	CTR-IV (1990-1998)		CTR-V (1998-2008)	
	Drugs	**Schedule**	**Drugs**	**Schedule**
Induction	Etoposide Cytarabine Daunorubicin	100 mg/m^2 d for 7 days 100 mg/m^2 c.i. d for 7 days 45 mg/m^2, days 1, 2 & 3.	Etoposide Cytarabine Daunorubicin	100 mg/m^2 d for 7 days 100 mg/m^2 c.i. d for 7 days 75 mg/m^2, days 1, 2 & 3.
Consolidation	Etoposide Cytarabine Daunorubicin	100 mg/m^2 d for 7 days 100 mg/m^2 c.i. d for 7 days 45 mg/m^2, days 1, 2 & 3. X 2	Etoposide Cytarabine Daunorubicin	100 mg/m^2 d for 7 days 100 mg/m^2 c.i. d for 7 days 60 mg/m^2, days 1, 2 & 3. X 1
Post Remission Therapy	Allogeneic or autologous transplantation		Allogeneic or autologous transplantation	

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Objectives of the Study

- Primary objectives:
  - Remission rate (CR: <5% blasts)
  - Rate of response with 1 course of therapy
- Secondary objectives
  - Proportion of patients undergoing stem cell transplantation
  - Outcomes after SCT
    - Allogeneic
    - Autologous
  - Causes of treatment failure
  - Overall survival

- Objectives of the current study (patients undergoing SCT)
  - Retrospectively review the outcome transplantation
  - Determine proportion of surviving patients
  - Review prognostic risks factors and define appropriate therapy in the South African context

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Patients and Methods

- Inclusion criteria
  - Age 13-65
  - Primary AML
  - No contraindications for SCT
- If HLA id. Sibling available: allo SCT
- If HLA id. Sibling not available: Auto SCT

- Exclusion criteria
  - AML evolving from MDS/MPO or chemotherapy/radiation
  - HIV infection
  - Severe organ dysfunction
  - History of recent myocardial infarction or active cardiac disease
  - APL (FAB M3)
  - Unable to mobilise enough CD34+ cells

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Conditioning for Transplantation

- Radiation based conditioning
  - TBI (fractionated) 1200 cGy
  - TLI (fractionated) 600 “
  - Cyclophosphamide 120 mg/kg
    - Neutropenic fever prophylaxis
    - Blood product support
- Chemotherapy based conditioning
  - Busulfan 12 mg/kg
  - Melphalan 140 mg/m^2
  - Cyclophosphamide 120 mg/kg
    - Neutropenic fever prophylaxis
    - Blood product support

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Stem cell Harvesting

- Bone marrow transplants
  - Collection by multiple aspirations
  - Buffy coat collected on IBM 2190
  - T-cell depletion
- PBPC transplants
  - Mobilization with G-CSF 5-10 ug daily, for 5-6 days
  - Aphaeresis until CD34+ > 2 x 10^6/kg
- GvHD prophylaxis: T-cell depletion
  - Campath antibodies used *in vitro*
    - 1-2mg/10^{10} cells
  - For PBPC grafts post transplant immunosuppression with cyclosporin for 90 days
- Autologous mobilisation of CD34+
  - Cyclophosphamide 60 mg/kg or Etoposide 2 gr/m^2
  - Filgrastim 300-600 ug/day
  - Large volume apheresis
  - Cryopreservation of the product
    - Controlled rate freezer

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Presentation Parameters

	All Patients N= 157	CTR-IV N= 71	CTR-V N= 86	P=
Age	35 (14-60)	33.5 (15-61)	36 (14-58)	NS
Sex (F/M)	78/79	39/32	39/47	NS
Hb g/dL	8.2(2.1-15)	9 (2.1-13.8)	7.2 (2.6-11.8)	0.07
WCC x 10^9/L	16.5 (0.6-414.5)	13.4 (0.6-179)	16.8 (0.7-145.6)	NS
Blasts x 10^9/L	7.27 (0-187)	4 (0-69)	8 (0-99)	NS
Platelets x 10^9/L	45.5 (3-2732)	48.5 (0-99)	40 (6-2732)	NS
LDH	672 (130-4185)	533 (166-3122)	750 (240-1499)	0.07
Cytogenetics Favourable Intermediate Unfavourable	N= 68	N= 28 24% 55% 21%	N= 42 22% 49% 29%	NS
PS	2 (1-4)	2 (1-4)	2 (1-4)	NS

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Response to Therapy

Initial Therapy	CTR-IV N= 71	CTR-V N= 86
Complete remission CR 1st course	44 (62%) 33	67 (78%; p= 0.02) 58
In CR failed to get SCT	15 (34%) 2 refused further Tx 2 cardiac dysfunction 2 platelet refractoriness 3 persistent infection 5 relapsed 1 unknown	21 (31%) 5 refused further Tx 2 cardiac dysfunction 5 sepsis 7 relapsed 1 failed SCT collection
Underwent SCT Allogeneic Autologous	29 11 18	45 23 22

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Stem Cell Transplantation

All: 74/111	Auto SCT N= 39	Allo SCT 35
Age	34 (14-65)	36 (15-58)
Females/Males	17	16
PS	2 (1-3)	2 (1-2)
CTR-IV/CTR-V	18 / 22	11 / 24
Cytogenetic risk Low Intermediate High	 11 (28%) 22 (56%) 6 (16%)	 8 (28%) 17 (49%) 10 (23%)
Hb g/dL WCC x 10^9/L Blasts x 10^9/L Plts x 10^9/L LDH i.u.	8.2 (5.9-15) 16.15 (0.72-414.5) 7.77 (0-80) 42 (17-2032) 630 (180-1150)	7.7 (6-15) 7.7 (6-15) 4.45 (0-80) 38 (17-2732) 313 (130-2121)
Median time to transplantation	69(41-402)	88(53-238)

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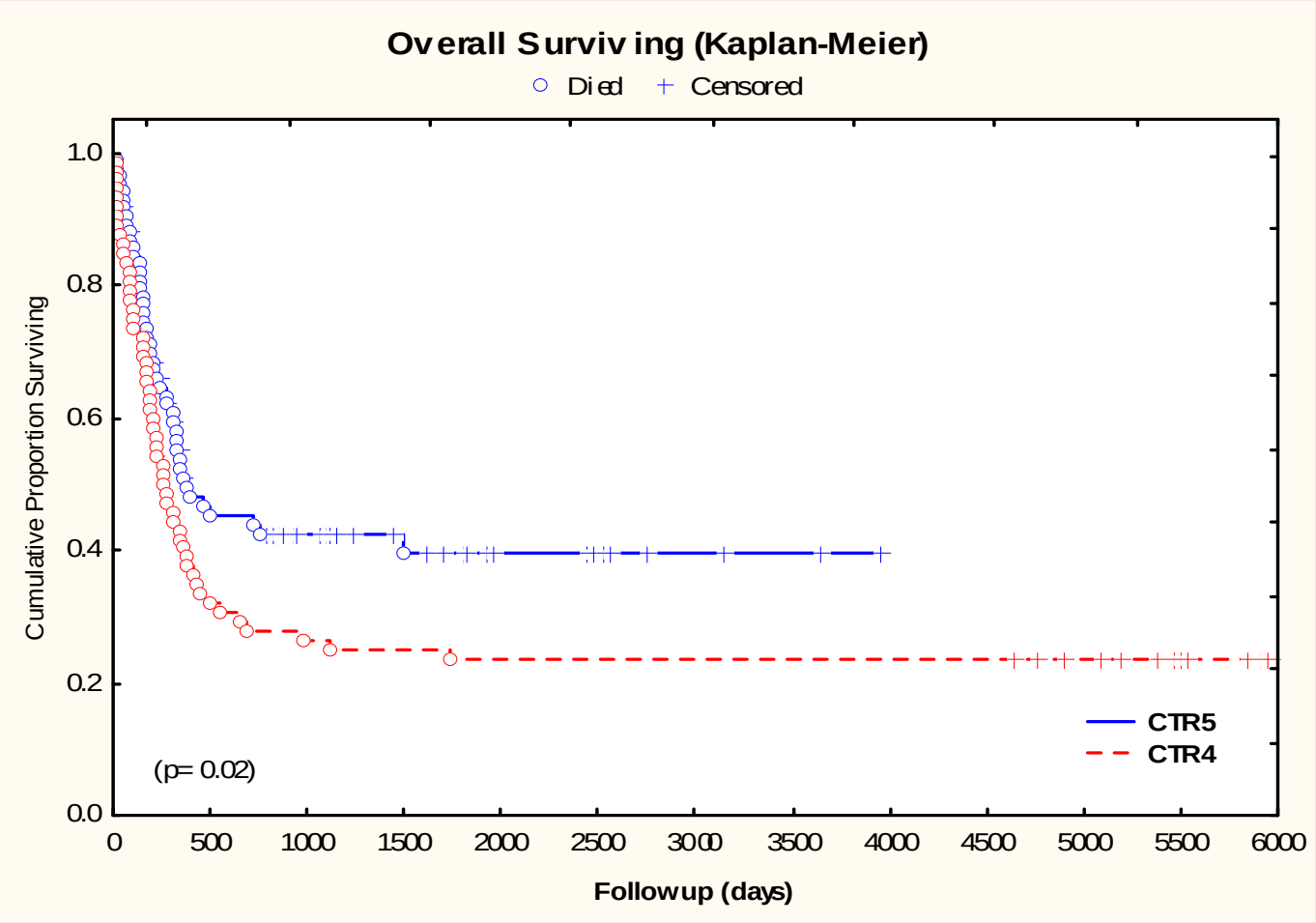
Treatment Outcome



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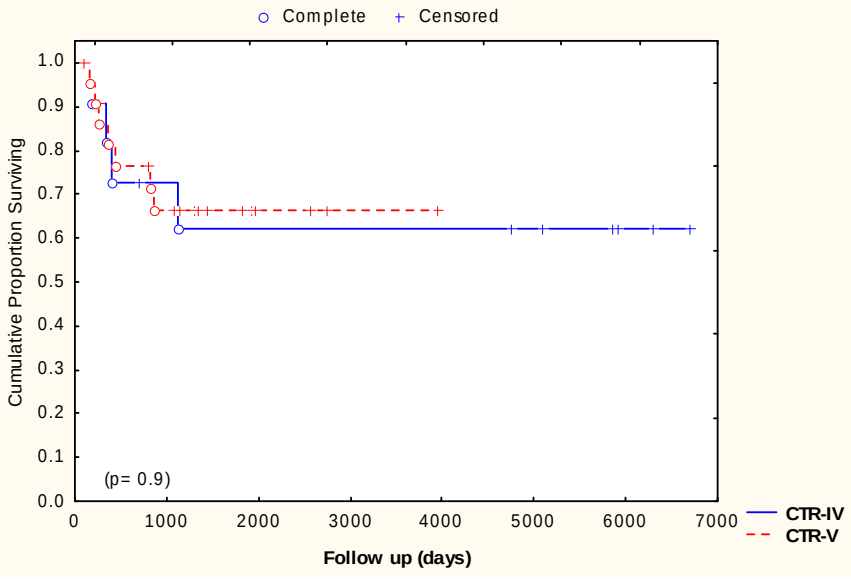
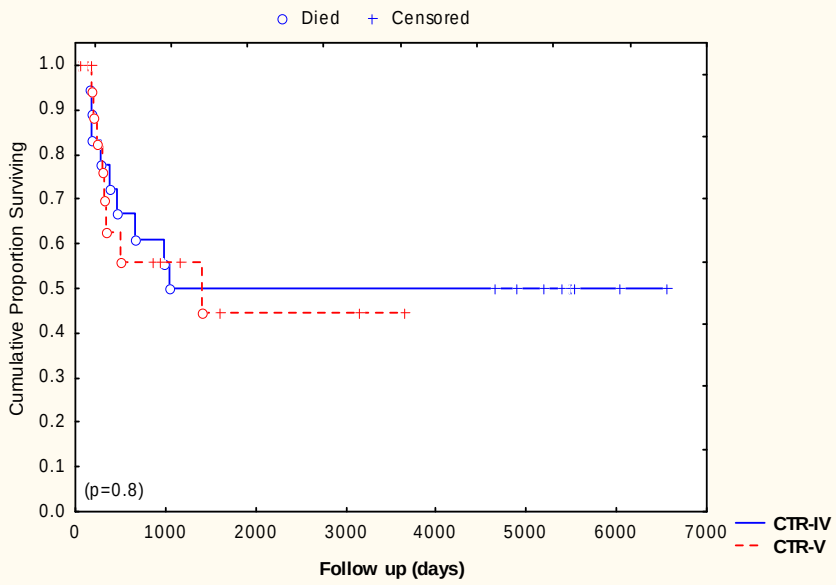
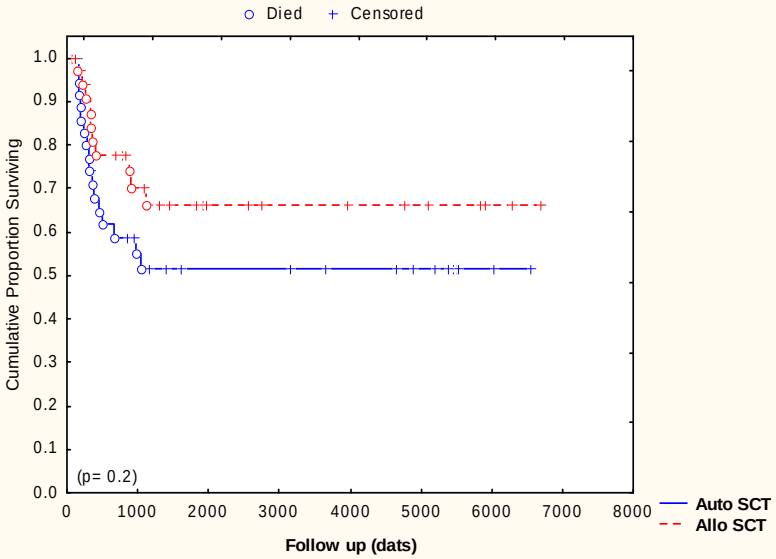
Allogeneic Stem Cell Transplantation
Outcome According to Trial



Autologous Stem Cell Transplantation
Survival According to Trial



Survival According to Type Transplant



Stem Cell Transplantation

Outcome of SCT	Auto SCT N= 39	Allo SCT= 35
Non relapse mortality VOD BM failure Malignancy Infections GvHD>1	7 (17%) 1 1 1 4	5 (14%) 1 4(2) 2
Relapses	9 (31%)	7 (23%)
Alive	23 (51%)	23 (66%)
OS	1609 (149- 6558)	1819 (83-6704)
Man-U-Whitney	Dysplasia Cytogenetics PS More than 1 induction course Blasts LDH	Dysplasia Cytogenetics PS More than 1 course
Cox Regression analysis	Cytogenetics (p= 0.012) LDH (p= 0.0019)	Cytogenetics (p= 0.012)

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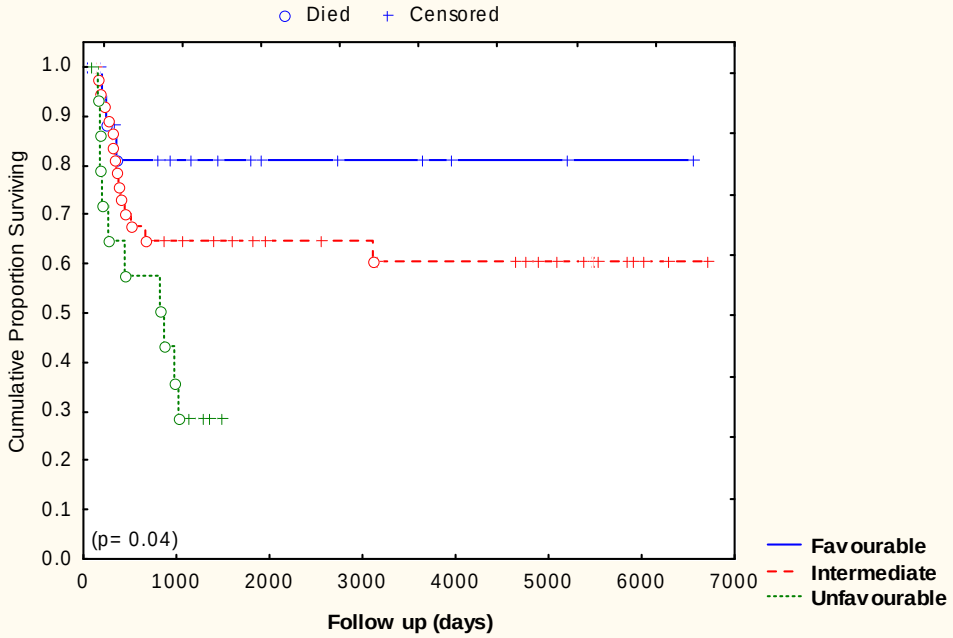
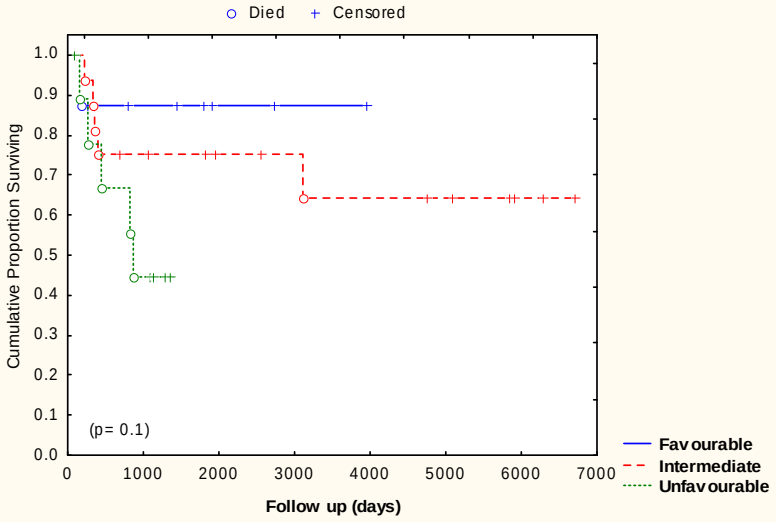
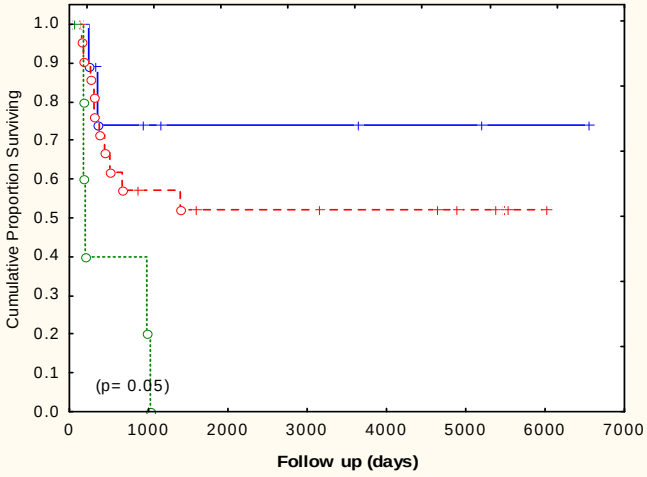
Stem Cell Transplantation
Survival Acording to Cytogenetic Risk



Allogeneic Transplantation
Survival According to Cyrogenetic Risk



Autologous Stem Cell Transplantation
Survival According to Cytogenetic Risk



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Conclusions:

1) Despite a proactive approach 1/3 of patients in CR 1 did not received the intended intensification
2) Cytogenetic profile is confirmed as a critical prognostic factor in de novo AML
3) Autologous stem cell transplantation is very effective consolidation therapy for patients with low cytogenetic risk
4) Patients undergoing Auto and Allo SCT appear to have similar outcome in intermediate risk cytogenetic group
5) Auto SCT has little protective role in patients with adverse karyotype AML

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Treatment of primary acute myeloid leukemia: results of a prospective multicenter trial including high-dose cytarabine or stem cell transplantation as post-remission strategy

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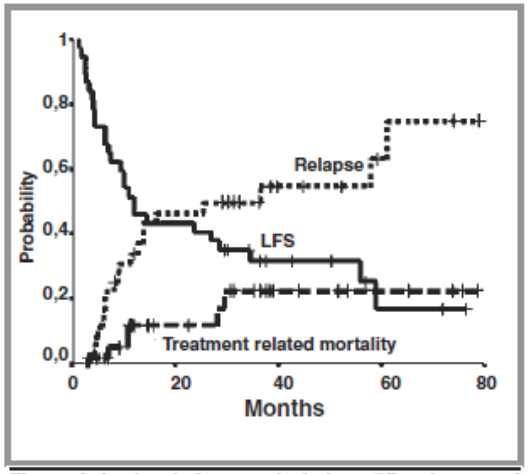


Figure 4. Leukemia-free survival since CR, relapse and TRM in patients > 50 years old according to the intention to treat with autologous transplantation (n=37).

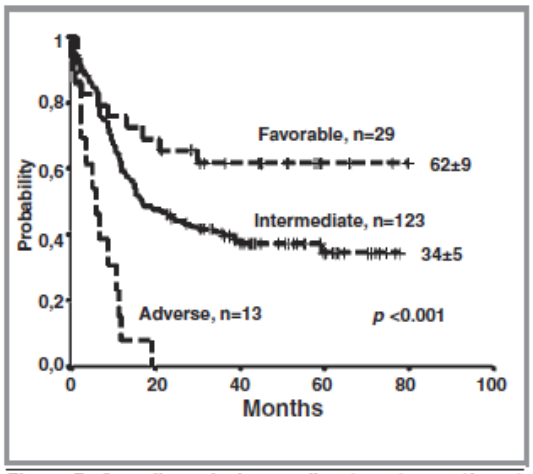
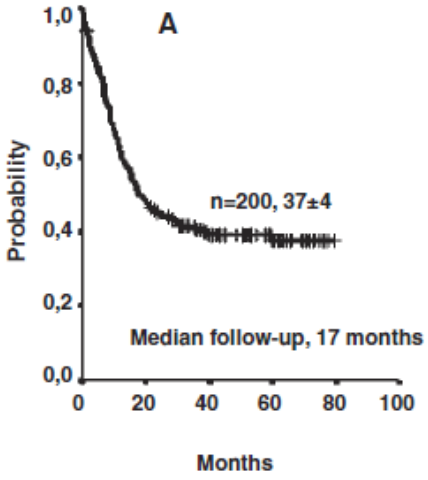
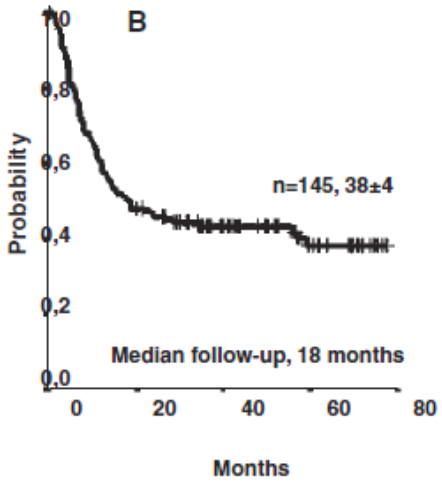


Figure 5. Overall survival according to cytogenetics at diagnosis.





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