Therapeutic leukoreduction and thromboreduction procedures in leukaemia and other blood cancers: who, why and how?

Professor John Snowden
Consultant Haematologist & BMT Programme Director
University of Sheffield, UK

The University Of Sheffield.

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

In hospital and in the community
proud to make a difference

June 2014

TREATMENTS: NEW HOSPITAL UNIT OFFERS THERAPY FOR RARE BLOOD DISORDERS

Centre to help save lives

BY RICHARD BLACKLEDGE
Health Reporter
richard.blackledge@thestar.co.uk

A centre offering vital therapies for people with life-threatening blood disorders has opened its doors in Sheffield.

The Royal Hallamshire Hospital's new therapeutic apheresis unit treats patients with conditions such as leukaemia and myeloma, running a 24-hour service.

It is also the only centre outside London which collects bone marrow stem cells for the Anthony Nolan charity.

Professor John Snowden, consultant haematologist and director of blood and marrow transplantation at Sheffield Teaching Hospitals, said the unit will 'help to save lives' – while patient Mark Ritson said the facility has made a 'huge difference'.

The centre has relocated within the Royal Hallamshire site, providing more space and a better environment for patients and staff.

Prof Snowden said that originally stem cells – which create new, healthy cells – could only be harvested by sucking bone marrow out of the pelvis.

But now complex machines draw blood from a donor's arm and filter out the stem cells, which are then transfused into the patient, 'homing in' on the bone marrow where they usually sit.

"For some diseases, the only chance of a cure is a stem cell transplant," said Prof Snowden.

Mark, aged 47, from Crookes in Sheffield, suffers from severe aplastic anaemia, where the bone marrow does not make enough new blood cells.

He has received a stem cell and bone marrow transplant for his condition.

"The outcome would have been very much worse had it not been for my treatment," said the dad-of-one, who runs an engineering firm.

"The stem cell transplant has saved my life and, I suspect, helped me to see my baby daughter grow up."

The unit is run by NHS Blood and Transplant and is one of six in England.

VIDEO

WATCH THE VIDEO AT THESTAR.CO.UK/VIDEO

JASON CHADWICK

Mark Ritson and Professor John Snowden in the new unit

Hyperleucocytosis

- WCC >100 x 10^9/L

- AML
- ALL
- CML
- CLL
- ‘Physiological’ leukaemoid reaction

Leukostasis – organs affected

- Lungs 80% - hypoxaemia and diffuse infiltrates
- CNS – confusion, stupor, headache, stroke, seizures, blurred vision, paplilloedema, retinal vein occlusion and haemorrhages
- Renal failure
- Others – myocardial infarction, peripheral ischaemia, priaprism

Also

- Profound metabolic abnormalities
- Tumour lysis syndrome…….
- Early death frequent

Mechanisms

- Raised blood viscosity?
- Endothelial adhesion of blasts
- Vascular occlusion and poor tissue perfusion
- Tissue infiltration
- Histology
  - Microvascular obstruction, dilated vessels
  - Leukaemic nodules surrounded by haemorrhage

BLOOD

The Journal of
The American Society of Hematology

VOL. 60, NO. 2 AUGUST 1982

BRIEF REVIEW

Hyperleukocytic Leukemias: Rheological, Clinical, and Therapeutic Considerations

By Marshall A. Lichtman and Jacob M. Rowe

BLOOD

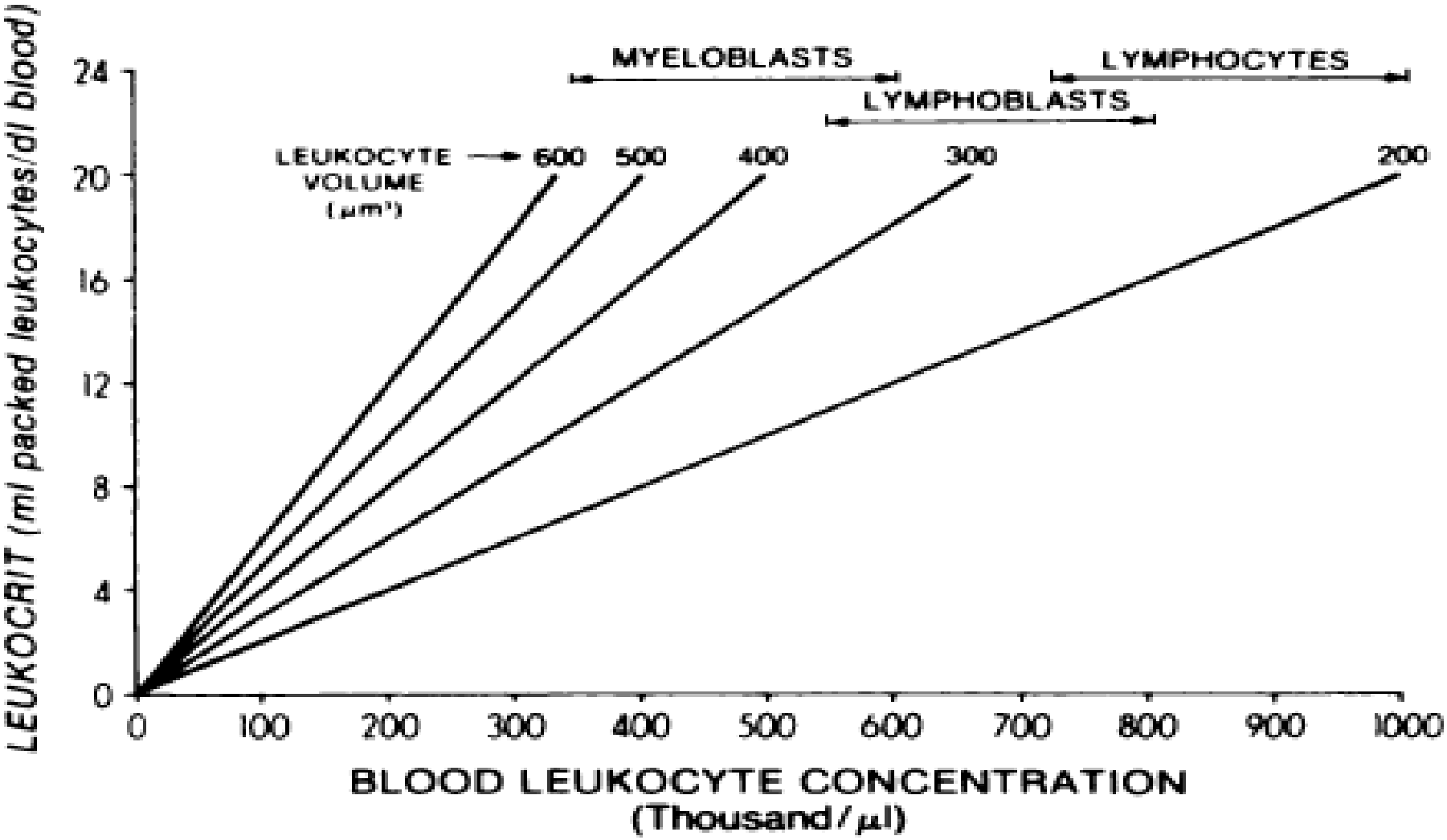
The Journal of
The American Society of Hematology

VOL. 60, NO. 2 AUGUST 1982

BRIEF REVIEW

Hyperleukocytic Leukemias: Rheological, Clinical, and Therapeutic Considerations

By Marshall A. Lichtman and Jacob M. Rowe



BLOOD

The Journal of
The American Society of Hematology

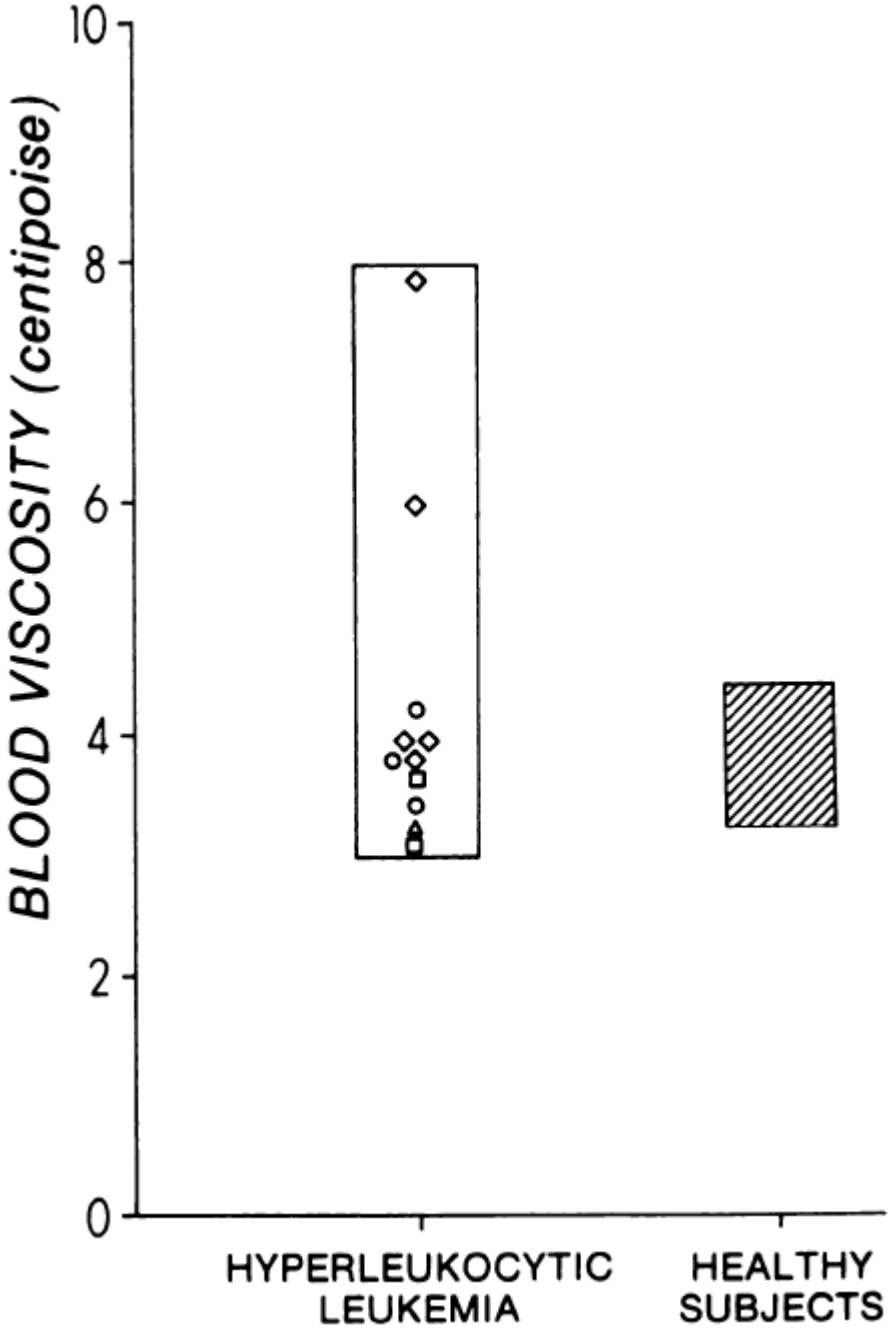
VOL. 60, NO. 2 AUGUST 1982

BRIEF REVIEW

Hyperleukocytic Leukemias: Rheological, Clinical, and Therapeutic Considerations

By Marshall A. Lichtman and Jacob M. Rowe

High white cell count does not always raise blood viscosity – also dependent on haematocrit (which may be low)



Endothelial cell activation by myeloblasts: molecular mechanisms of leukostasis and leukemic cell dissemination

Anne Stucki, Anne-Sophie Rivier, Milica Gikic, Natacha Monai, Marc Schapira, and Olivier Spertini

Leukostasis and tissue infiltration by leukemic cells are poorly understood life-threatening complications of acute leukemia. This study has tested the hypothesis that adhesion receptors and cytokines secreted by blast cells play central roles in these reactions. Immunophenotypic studies showed that acute myeloid leukemia (AML) cells (n = 78) of the M0 to M5 subtypes of the French-American-British Cooperative Group expressed various amounts of adhesion receptors, including CD11a, b, c/CD18, CD49d, e, f/CD29, CD54, sCD15, and L-selectin. The presence of functional adhesion receptors was evaluated using a nonstatic adhesion assay. The number of blast cells attached to unactivated endothelium increased by 7 to 31 times after a 6-hour exposure of endothelium to tumor necrosis factor (TNF)-α. Inhibition studies showed that multiple adhesion receptors—including L-selectin, E-selectin, VCAM-1, and CD11/CD18—were involved in blast cell adhesion to TNF-α–activated endothelium. Leukemic cells were then cocultured at 37°C on unactivated endothelial cell monolayers for time periods up to 24 hours. A time-dependent increase in the number of blasts attached to the endothelium and a concomitant induction of ICAM-1, VCAM-1, and E-selectin were observed. Additional experiments revealed that endothelial cell activation by leukemic myeloblasts was caused by cytokine secretion by blast cells, in particular TNF-α and IL-1β, and direct contacts between adhesion receptors expressed by blast cells and endothelial cells. Thus, leukemic cells have the ability to generate conditions that promote their own adhesion to vascular endothelium, a property that may have important implications for the pathophysiology of leukostasis and tissue infiltration by leukemic blast cells. (Blood. 2001;97:2121-2129)

AML

- 5-18%
- FAB types M4 & M5 in most
- Flt-3 and MLL

- Cells large and more rigid

- Up regulated adhesion – ICAM-1, VCAM-1, E-selectin
- Increased cytokine secretion – IL-1B, TNF-B

ALL

- Cells small to medium size (L1-L3 morphology)
- Haemoglobin level classically ‘preserved’ in ALL – perhaps more of factor in hyperviscosity
- Less data about adhesion molecules, endothelial interactions ?less sticky
- ALL more common in paediatric population

  ?better tolerance of hyperleucocytosis

CML

- Variable size and maturity of circulating cells
- More deformable
- Hyperleucocytosis commoner in paediatric CML
- Hyperleucocytosis more significant in blast crisis vs chronic phase CML

CLL and NHL

- WCC may commonly be above 100 $x10^9$/L with no clinical features of leucostasis
- Some patients remain stable and untreated despite very high cell counts
- Cells small, deformable, probably don't adhere, obstruct etc

Physiological hyperleukocytosis/ leukaemoid reaction

- Rare to have leukostasis or any clinical problems directly related to the high WCC, if at all…..

What is the role of leukapheresis in hyperleukocytosis?

Risk:benefit ratio?

- What are the risks of hyperleukocytosis and leukostasis in the interval before chemotherapy starts to work?
- What are the risks of performing apheresis (and costs) whilst chemotherapy starts to work?
- What is the evidence of benefit of apheresis?

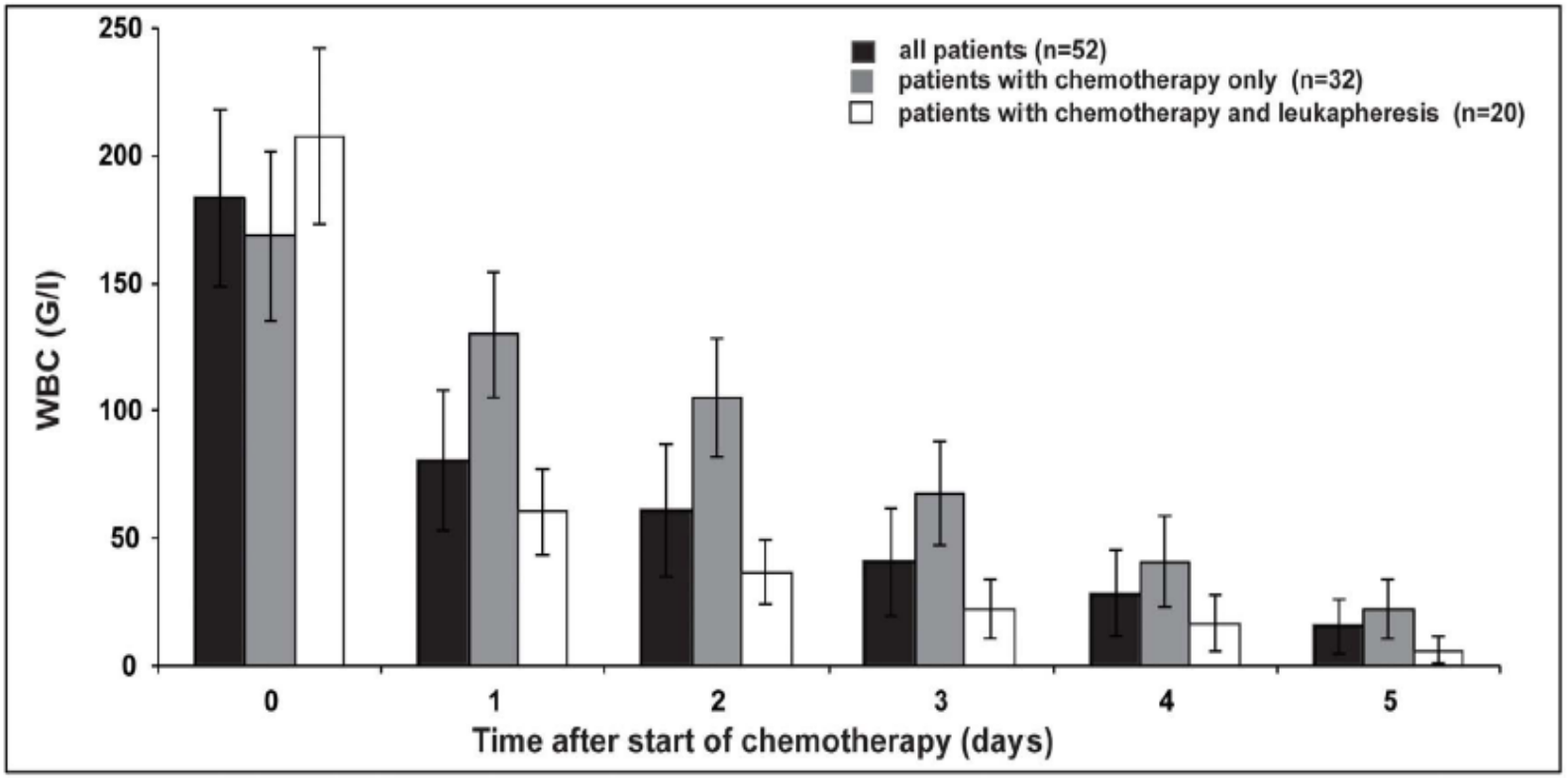
Risks of leukapheresis

- Central or femoral line placement
- Volume disturbances
- Electrolyte disturbances
- Infections and bleeding
- Added to risks of often unstable patient

- Delays to chemotherapy +/- ?washing out
- Costly

Measurable benefits of apheresis

Greater reduction in WCC with apheresis



Pastore et al, PLOS One 2014; 9:1-11

BUT…

- Generally less than expected based on collection bag counts
  - presumably because of mobilization of blasts from endothelium, and organs, such as bone marrow, spleen etc

- Does this reduce the impact of leukopheresis?

British Journal of Haematology, 1997, 98, 433–436

SHORT REPORT

Therapeutic leukapheresis in hyperleucocytic leukaemias: lack of correlation between degree of cytoreduction and early mortality rate

PIERLUIGI PORCU,[1] CONSTANCE F. DANIELSON,[2] ATTILIO ORAZI,[2] NYLA A. HEEREMA,[3] THEODORE G. GABIG[1] AND LEO J. MCCARTHY[3] *Departments of* [1]*Medicine,* [2]*Pathology, and* [3]*Medical Genetics, Indiana University Medical Center, Indianapolis, Indiana, U.S.A.*

Received 4 April 1997; accepted for publication 21 April 1997

Leukocytoreduction according to outcome

	Death within 1 week 14/48 (29·1%)	Survival at 1 week 34/48 (70·9%)	*P* value
Percent reduction (%)			
Median	57·4	55·7	>0·2
Range	3·5–91·2	13·7–93·5	
Absolute reduction ($\times 10^9$/l)			
Median	124	116	>0·2
Range	8–301	23–364	
Final WBC count ($\times 10^9$/l)			
Median	91	94	>0·2
Range	21–374	10–321	

Effect of leukapheresis - evidence?

Improved cerebral perfusion in a case report

- Kasner et al, Am J Haematol 2007

- Patient AML + meningioma encasing left internal carotid artery

- Hyperleukocytosis with symptoms of cerebral ischaemia

- Transcranial Doppler ultrasound
  - increased flow velocities in the left internal carotid and the right middle cerebral arteries pre-leukapheresis
  - normalized after leukapheresis

Effect of leukapheresis – evidence?

Retrospective studies, intrinsic biases

- Reduces early mortality (but not overall survival)
  - Thiebaut et al, Ann Haematol 2000
  - Giles et al, Leuk Lymphoma 2001
  - Bug et al, Transfusion 2007
  - + others…

- Makes no impact on early (or late) mortality
  - Porcu et al, BJH 1997
  - Pastore et al, PlosOne 2014
  - + others…

Impact of leukapheresis on early death rate in adult acute myeloid leukemia presenting with hyperleukocytosis

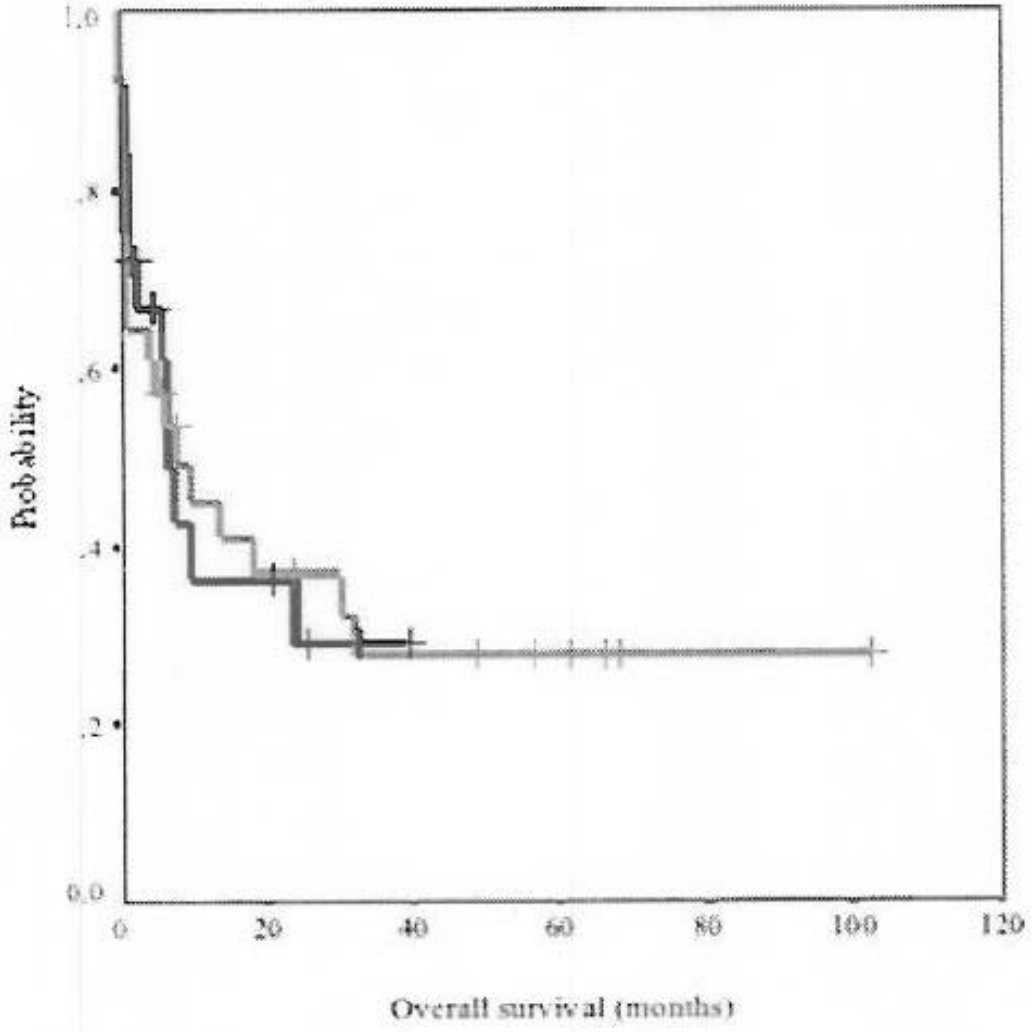
Gesine Bug, Konstantinos Anargyrou,* Torsten Tonn, Heike Bialleck, Erhard Seifried, Dieter Hoelzer, and Oliver G. Ottmann*

- 53 patients AML and hyperleucocytosis >100 $x10^9$/L from 1995-2005 analysed retrospectively
- Before 2001 all pts received chemo only (n=28)
- After 2001 all pts received LA + chemo (n=25)
- Multivariate analysis: risk of early death
  - LA + chemo 16%
  - Chemo only 32%
  - p=0.015

Transfusion 2007, 47; 1843-1850

Impact of leukapheresis on early death rate in adult acute myeloid leukemia presenting with hyperleukocytosis

Gesine Bug, Konstantinos Anargyrou,* Torsten Tonn, Heike Bialleck, Erhard Seifried, Dieter Hoelzer, and Oliver G. Ottmann*



Overall survival similar: leukapheresis had no impact on overall survival (p=NS)

Transfusion 2007, 47; 1843-1850

OPEN ACCESS Freely available online

PLOS | ONE

The Role of Therapeutic Leukapheresis in Hyperleukocytotic AML

Friederike Pastore[1,3,4]*, Alessandro Pastore[1], Georg Wittmann[2], Wolfgang Hiddemann[1,3,4], Karsten Spiekermann[1,3,4]

1 Department of Internal Medicine III, University Hospital Munich, Ludwig-Maximilians-University Munich - Campus Großhadern, Munich, Germany, **2** Department of Transfusion Medicine, University Hospital Munich, Ludwig-Maximilians-University Munich - Campus Großhadern, Munich, Germany, **3** German Cancer Consortium (DKTK), Heidelberg, Germany, **4** German Cancer Research Center (DKFZ), Heidelberg, Germany

- 52 patients median age 60 presenting with WCC >100 x10^9/L
  - 20 patients leukapheresis + chemotherapy
  - 32 patients chemotherapy only
- Significantly greater reduction in WCC with leukapheresis vs chemo ($p<0.001$)

OPEN ACCESS Freely available online

PLOS | ONE

The Role of Therapeutic Leukapheresis in Hyperleukocytotic AML

Friederike Pastore[1,3,4]*, Alessandro Pastore[1], Georg Wittmann[2], Wolfgang Hiddemann[1,3,4], Karsten Spiekermann[1,3,4]

1 Department of Internal Medicine III, University Hospital Munich, Ludwig-Maximilians-University Munich - Campus Großhadern, Munich, Germany, **2** Department of Transfusion Medicine, University Hospital Munich, Ludwig-Maximilians-University Munich - Campus Großhadern, Munich, Germany, **3** German Cancer Consortium (DKTK), Heidelberg, Germany, **4** German Cancer Research Center (DKFZ), Heidelberg, Germany

	All (n=52)		LA/Chemo (n=20)		Chemo (n=32)		P LA/Chemo vs Chemo
endpoint	n	%	n	%	n	%	
Death							
≤24 hours	5	10	4	20	1	3	0.045
≤7 days	9	17	6	30	3	9	0.056
≤28 days	13	25	6	30	7	22	n.s.
≤100 days	19	37	7	35	12	38	n.s
≤ last follow up	25	48	10	50	15	47	n.s.
Adequate early blast clearance (n=45)	28	62	9	56	19	66	n.s.
Complete remission (n=47)	25	53	8	50	17	55	n.s.
Relapse (n=25)	13	52	4	50	9	53	n.s.

- Patients undergoing leukapheresis had higher 24 hour death rate!

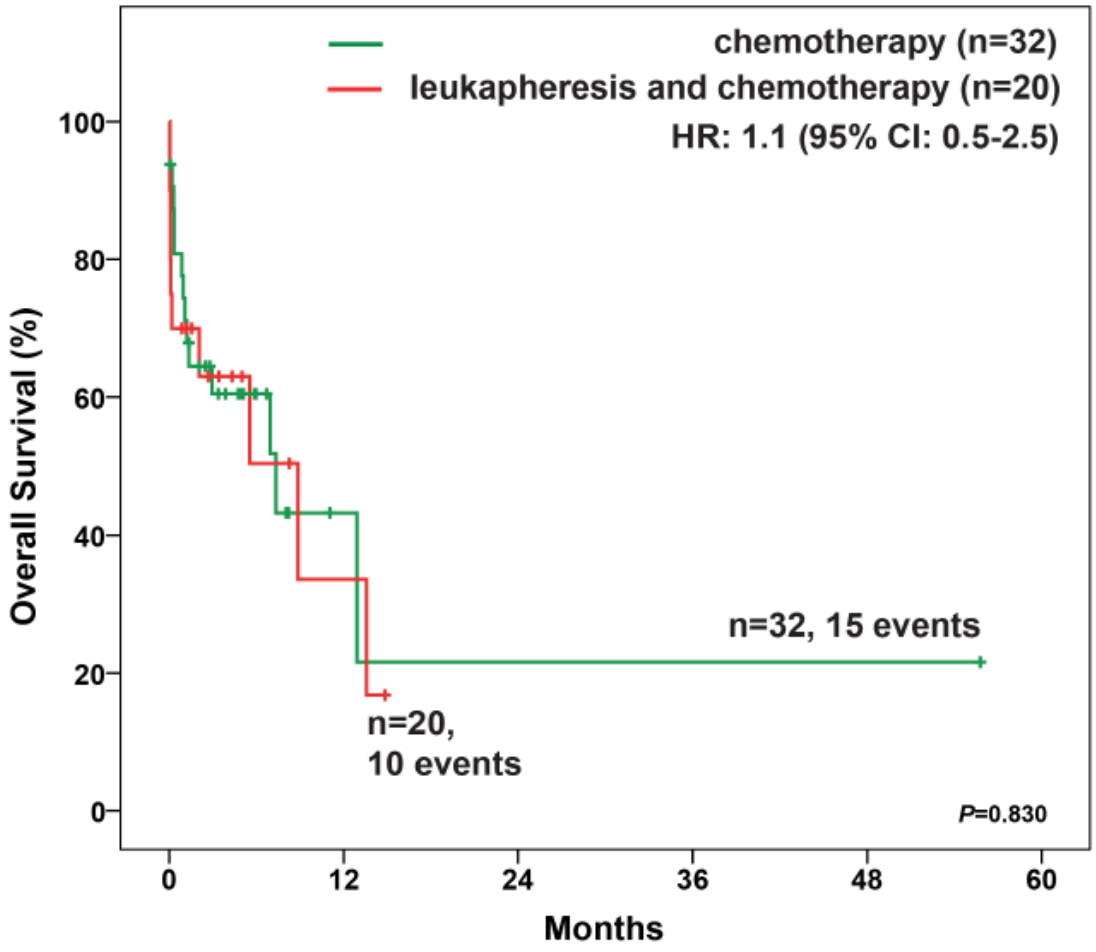
OPEN ACCESS Freely available online

PLOS ONE

The Role of Therapeutic Leukapheresis in Hyperleukocytotic AML

Friederike Pastore[1,3,4]*, Alessandro Pastore[1], Georg Wittmann[2], Wolfgang Hiddemann[1,3,4], Karsten Spiekermann[1,3,4]

1 Department of Internal Medicine III, University Hospital Munich, Ludwig-Maximilians-University Munich - Campus Großhadern, Munich, Germany, **2** Department of Transfusion Medicine, University Hospital Munich, Ludwig-Maximilians-University Munich - Campus Großhadern, Munich, Germany, **3** German Cancer Consortium (DKTK), Heidelberg, Germany, **4** German Cancer Research Center (DKFZ), Heidelberg, Germany



OPEN ACCESS Freely available online

PLOS ONE

The Role of Therapeutic Leukapheresis in Hyperleukocytotic AML

Friederike Pastore[1,3,4]*, Alessandro Pastore[1], Georg Wittmann[2], Wolfgang Hiddemann[1,3,4], Karsten Spiekermann[1,3,4]

1 Department of Internal Medicine III, University Hospital Munich, Ludwig-Maximilians-University Munich - Campus Großhadern, Munich, Germany, 2 Department of Transfusion Medicine, University Hospital Munich, Ludwig-Maximilians-University Munich - Campus Großhadern, Munich, Germany, 3 German Cancer Consortium (DKTK), Heidelberg, Germany, 4 German Cancer Research Center (DKFZ), Heidelberg, Germany

- Leukapheresis + chemotherapy group had significantly worse:
  - Troponin (p=0.01)
  - Thromboplastin time (p=0.005)
  - Antithrombin (p=0.002)
  - Dyspnoea (p=0.001)
  - Oxygen requirement (p=0.008)
  - Neurological degeneration (p=0.011)

- Developed a risk score and used multivariate analysis to balance groups but even with this leukapheresis did not change early mortality

Paediatric ALL

Lowe et al, Pediatr Blood Cancer 2005;45:10–15

- 178 ALL patients (median age 7.1 yrs) WCC>200 $x10^9$/L
- Degree of hyperleukocytosis >400 $x10^9$/L associated with
  - Increased neurological complications (p=0.006)
  - Increased respiratory complications (p=0.014)
- 94 with median WBC >400 $x10^9$/L had leukapheresis
  - Reduced WCC significantly (p=0.013)
  - induction chemotherapy delayed significantly (p=0.013)

- Conclusion: leukapheresis for WCC >400 $x10^9$/L in all, but also at lower levels if complications

Journal of Clinical Apheresis 25:83–177 (2010)

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice–Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

Zbigniew M. Szczepiorkowski,[1*†] Jeffrey L. Winters,[2*] Nicholas Bandarenko,[3*] Haewon C. Kim,[4*] Michael L. Linenberger,[5*] Marisa B. Marques,[6*] Ravindra Sarode,[7*] Joseph Schwartz,[8*] Robert Weinstein,[9*] and Beth H. Shaz[10*]

HYPERLEUKOCYTOSIS

Incidence of hyperleukocytosis at diagnosis	Procedure	Recommendation	Category
AML, WBC $>100 \times 10^9$/L: $\leq$18%	Leukocytapheresis	Grade 1B	I (leukostasis)
ALL, WBC $>400 \times 10^9$/L: $\leq$3%	Leukocytapheresis	Grade 2C	III (prophylaxis)

# of reported patients*: > 300

	RCT	CT	CS	CR	Type of evidence
Acute myeloid leukemia	0	5 (385)	6 (184)	7 (9)	Type II-2
Acute lymphoblastic leukemia	0	3 (366)	3 (39)	NR	Type II-2

TABLE I. Indications for Therapeutic Apheresis—ASFA 2010 Categories[a]

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. [Example: plasma exchange in Guillain-Barré syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition].
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment. [Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease]
III	Optimum role of apheresis therapy is not established. Decision making should be individualized. [Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure].
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances. [Example: plasma exchange for active rheumatoid arthritis].

TABLE II. Level of Evidence Used in the ASFA Special Issue 2010[a]

Evidence level	Evidence quality
Type I	Obtained from at least one properly designed randomized controlled trial
Type II-1	Obtained from a well-designed controlled trials without randomization
Type II-2	Obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
Type II-3	Obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence
Type III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Szczepiorkowski et al. Journal of Clinical Apheresis 2010

Journal of Clinical Apheresis 25:83–177 (2010)

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice–Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

Zbigniew M. Szczepiorkowski,[1*†] Jeffrey L. Winters,[2*] Nicholas Bandarenko,[3*] Haewon C. Kim,[4*] Michael L. Linenberger,[5*] Marisa B. Marques,[6*] Ravindra Sarode,[7*] Joseph Schwartz,[8*] Robert Weinstein,[9*] and Beth H. Shaz[10*]

HYPERLEUKOCYTOSIS

Incidence of hyperleukocytosis at diagnosis	Procedure	Recommendation	Category
AML, WBC >100 × 10^9/L: ≤18%	Leukocytapheresis	Grade 1B	I (leukostasis)
ALL, WBC >400 × 10^9/L: ≤3%	Leukocytapheresis	Grade 2C	III (prophylaxis)

# of reported patients*: > 300

	RCT	CT	CS	CR	Type of evidence
Acute myeloid leukemia	0	5 (385)	6 (184)	7 (9)	Type II-2
Acute lymphoblastic leukemia	0	3 (366)	3 (39)	NR	Type II-2

Thrombocytosis

- Thrombocytosis - platelet count >450-500 $x10^9$/L
- Most commonly secondary to acute bleeding, haemolysis, infection, inflammation, asplenia, cancer or iron deficiency
  - increased normal platelets do not predispose to thrombosis or bleeding
- Myeloproliferative neoplasms (MPNs) have functionally abnormal platelets and causally linked
  - Thrombosis
  - Bleeding
- Splenectomy
  - routine indications
  - performed for palliation of pain or cytopenias in MPN associated with extreme ‘‘rebound’’ thrombocytosis in 5% of cases, with post-operative thrombosis (10%) and bleeding (14%)

Thrombocytosis in MPD: paradoxical bleeding diathesis

- Reduced levels of high molecular weight von Willebrand multimers in plasma during extreme thrombocytosis

- Normalisation of platelet function after thrombocytapheresis

van Genderen et al Br J Haem 1997
Orlin & Berkman, Transfusion 1980

Thrombocytapheresis

- Myeloproliferative disorders to prevent
  - thrombotic complications
  - haemorrhagic complications
  - splenectomy management – ‘rebound’

- In some reports:
  - in pregnancy and delivery when use of cytoreductive agents is contraindicated
  - where a rapid decrease in platelet count is needed before surgery
  - in severe ischaemic complications unresponsive to antithrombotic therapy
  - in patients who developed severe secondary thrombocytosis after splenectomy or other causes

Much of the evidence is old or anecdotal……..

Plateletpheresis in the Management of Thrombocytosis

By Edwin G. Taft, Robert B. Babcock, William B. Scharfman, and Anthony P. Tartaglia

Acute thrombotic and hemorrhagic manifestations of thrombocytosis associated with myeloproliferative disorders may be life threatening. Conventional therapy with radioisotopes and/or cytotoxic drugs may require weeks for effective control of platelet counts. In five patients, plateletpheresis by discontinuous-flow (Haemonetics) or continuous-flow (Aminco Celltrifuge) centrifugation was used as a means of reducing platelet counts acutely. With each procedure, approximately $2–9 \times 10^{12}$ platelets were removed, resulting in decrements in platelet counts and relief of symptoms. Plateletpheresis is a useful and safe acute means of controlling platelet counts in myeloproliferative disorders.

Blood, Vol. 50, No. 5 (November), 1977

Journal of Clinical Apheresis 25:83–177 (2010)

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice–Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

Zbigniew M. Szczepiorkowski,[1*†] Jeffrey L. Winters,[2*] Nicholas Bandarenko,[3*] Haewon C. Kim,[4*] Michael L. Linenberger,[5*] Marisa B. Marques,[6*] Ravindra Sarode,[7*] Joseph Schwartz,[8*] Robert Weinstein,[9*] and Beth H. Shaz[10*]

THROMBOCYTOSIS

Incidence: 0.59-2.53 per 100,000/year	**Procedure**	**Recommendation**	**Category**
essential thrombocythemia (ET);	Thrombocytapheresis	Grade 2C	II (symptomatic thrombocytosis)
0.02-2.8 per 100,000/year polycythemia vera (PV)	Thrombocytapheresis	Grade 2C	III (prophylaxis or secondary thrombocytosis)
Prevalence: 22-24 per 100,000 for ET and PV			

# of reported patients*: 100-300

	RCT	CT	CS	CR	Strength of evidence
Myeloproliferative neoplasms	0	0	7 (180)	22 (27)	Type II-3
Secondary thrombocytosis	0	0	2 (39)	3 (4)	Type II-3

TABLE I. Indications for Therapeutic Apheresis—ASFA 2010 Categories[a]

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment. [Example: plasma exchange in Guillain-Barré syndrome as first-line standalone therapy; plasma exchange in myasthenia gravis as first-line in conjunction with immunosuppression and cholinesterase inhibition].
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment. [Example: plasma exchange as standalone secondary treatment for acute disseminated encephalomyelitis after high-dose IV corticosteroid failure; extracorporeal photopheresis added to corticosteroids for unresponsive chronic graft-versus-host disease]
III	Optimum role of apheresis therapy is not established. Decision making should be individualized. [Example: extracorporeal photopheresis for nephrogenic systemic fibrosis; plasma exchange in patients with sepsis and multiorgan failure].
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances. [Example: plasma exchange for active rheumatoid arthritis].

TABLE II. Level of Evidence Used in the ASFA Special Issue 2010[a]

Evidence level	Evidence quality
Type I	Obtained from at least one properly designed randomized controlled trial
Type II-1	Obtained from a well-designed controlled trials without randomization
Type II-2	Obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group
Type II-3	Obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence
Type III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Szczepiorkowski et al. Journal of Clinical Apheresis 2010

Journal of Clinical Apheresis 25:83–177 (2010)

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice–Evidence-Based Approach from the Apheresis Applications Committee of the American Society for Apheresis

Zbigniew M. Szczepiorkowski,[1*†] Jeffrey L. Winters,[2*] Nicholas Bandarenko,[3*] Haewon C. Kim,[4*] Michael L. Linenberger,[5*] Marisa B. Marques,[6*] Ravindra Sarode,[7*] Joseph Schwartz,[8*] Robert Weinstein,[9*] and Beth H. Shaz[10*]

THROMBOCYTOSIS

Incidence: 0.59-2.53 per 100,000/year	**Procedure**	**Recommendation**	**Category**
essential thrombocythemia (ET);	Thrombocytapheresis	Grade 2C	II (symptomatic thrombocytosis)
0.02-2.8 per 100,000/year polycythemia vera (PV)	Thrombocytapheresis	Grade 2C	III (prophylaxis or secondary thrombocytosis)
Prevalence: 22-24 per 100,000 for ET and PV			

# of reported patients*: 100-300

	RCT	CT	CS	CR	Strength of evidence
Myeloproliferative neoplasms	0	0	7 (180)	22 (27)	Type II-3
Secondary thrombocytosis	0	0	2 (39)	3 (4)	Type II-3

Thrombocytapheresis

- Question to the floor!
- How often have you done it?

- Sheffield NHSBT Regional Apheresis Centre
  - 0 cases in 14 years (personal communication Dr Khaled El-Ghariani NHSBT Sheffield since 2000)

Cytapheresis in Pregnancy/Delivery

- Chemotherapy generally avoided in first trimester because of concerns of teratogenicity, although interferon acceptable
- Chemotherapy may be given later in pregnancy and delivery may be brought forward to permit definitive treatment
- Control of WCC or platelet counts in pregnancy with apheresis reported in cases/series – most commonly in CML and MPD

Grey cases

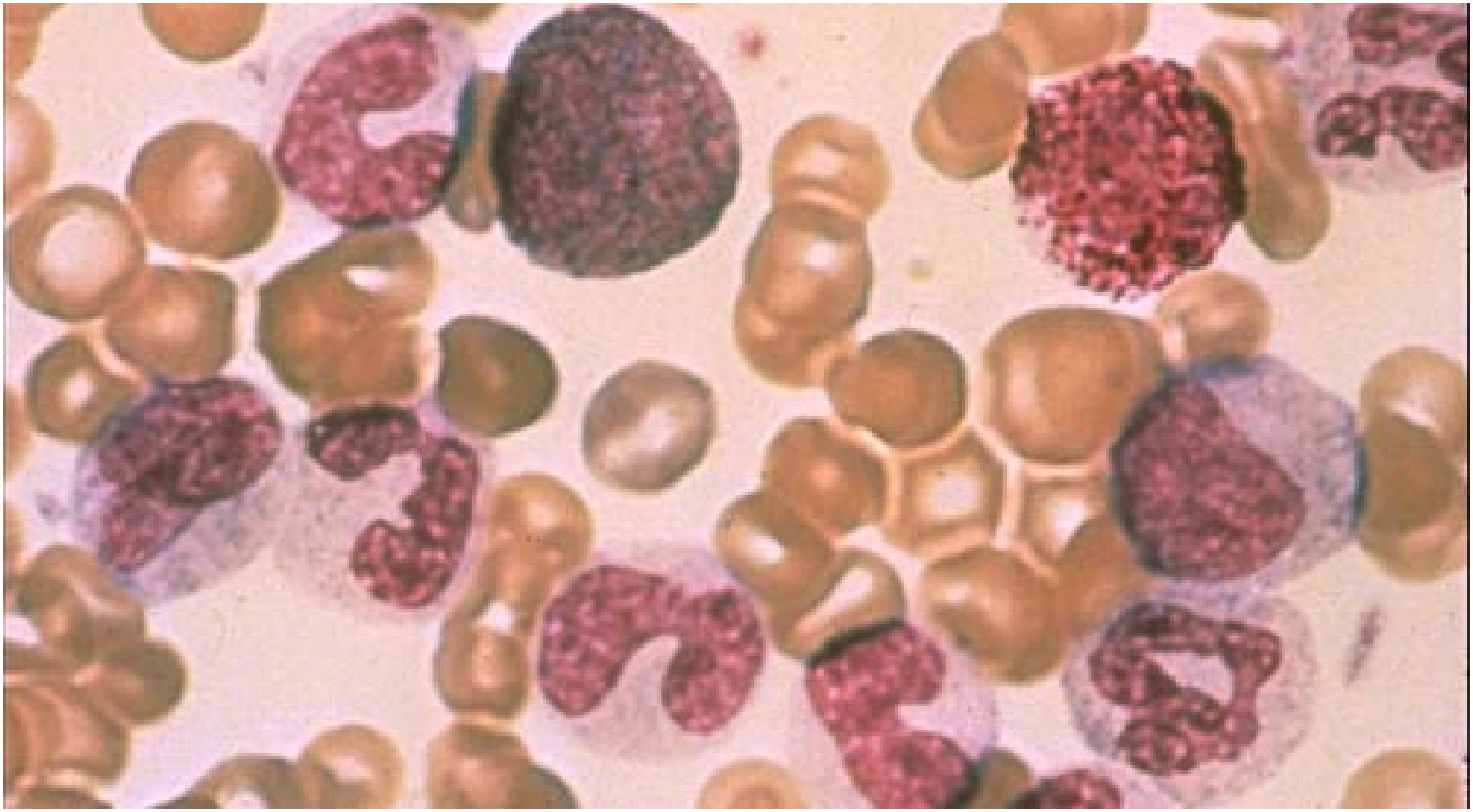
Leukapheresis – would you do the same?

Grey case 1

8/2/11

- 23 year old university student
- Unwell 2 months
- Fatigue, weight loss, abdominal distension, headache, blurring of vision, sweating, dizziness on standing, venous distension on forehead
- On examination – pale, cachectic, massive hepatosplenomegaly, distended neck veins, fundi engorged vessels with small haemorrhage

Hb 89g/L, plts 372 $x10^9$/L
WCC 558$x10^9$/L: neuts 260, eos 23, baso 17, blasts 7, NRBC 5, mono 1.9$x10^9$/L
BCR-ABL subsequently confirmed CML



Grey case 1: Management

- IV fluids
- Leukapheresis #1 8/2/11 WCC 669 $x10^9/L$
- Hydroxycarbamide 3g day with rasburicase
- Leukapheresis #2 9/2/11 WCC 498 $x10^9/L$
- Leukapheresis #3 10/2/11 WCC 378 $x10^9/L$
- Patient feeling better
- 12/2/11 WCC 355 $x10^9/L$
- 10/2/11 WCC 251 $x10^9/L$
- Thereafter imatinib, nilotinib and eventual allograft

Grey case 2

14/6/2014

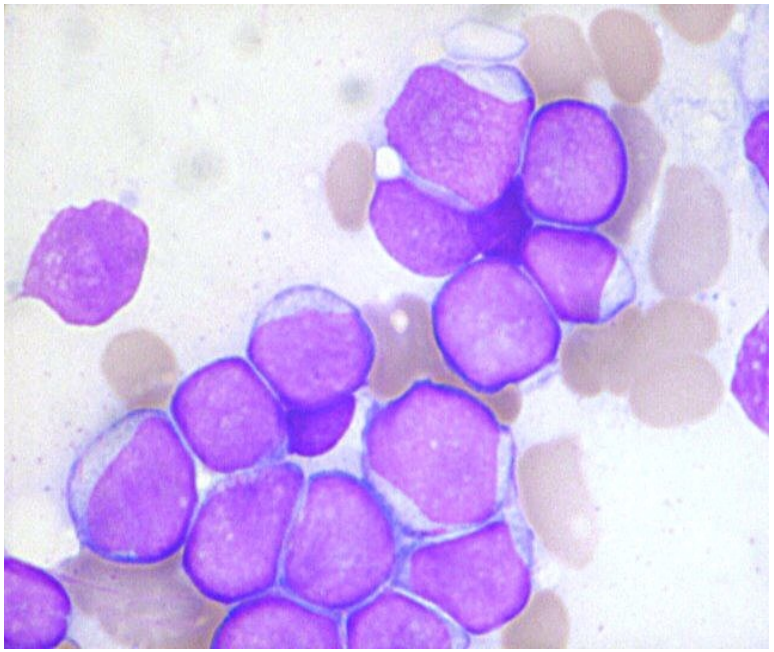
- 63 year old female

- Admission via A&E with generalised weakness, reduced appetite, impetigo, diarrhoea, coryzal symptoms, cough, gum hypertrophy

- Collapsed in A&E waiting room

Grey case 2

- Hb 80g/L, plts 67 $x10^9$/L
- WCC 184 $x10^9$/L – monocytoid cells, promonocytes, blasts - AML M5



Grey case 2

14/6/2014

- Creat 224 micromol/L – new
- RR 30-35/ min, O2 sats 90% on air
- Lung fields clear on auscultation
- CXR – clear
- ECG – sinus tachycardia

Grey case 2

14-15/06/14

- iv broad spectrum antibiotics and fluids, catheterised
- Rasburicase
- Hydroxycarbamide 1g tds

Grey case 2

15/5/14

- Increasing oxygen demand - 95% ON 60% O2
- ABGs O2 8.11 CO2 3.61
- CXR L sided basal consolidation
- Admitted to ITU
- Metraminol for hypotension
- Leukapheresis performed - WCC reduced to 88.2 $x10^9/L$
- Stabilised further re sepsis, ongoing hydroxycarbamaide
- Started intensive chemotherapy (DA50) on 20/6/14

Conclusions: Who, why and how?

Who?

- Currently any patient with features of symptomatic leucostasis or thrombocytosis, if can tolerate procedure
  - Probably not be worth the risk:benefit ratio, delays and costs if just hyperleucocytosis and thrombocytosis
  - No robust evidence-based ‘criteria’ for leucostasis or thrombocytosis
  - Usually part of complex clinical picture

Conclusions: Who, why and how?

Why?

- Some evidence suggests benefit
- Some evidence neutral
- Quality of evidence on either front not high

Conclusions: Who, why and how?

How…are we going to improve clinical decision making?

- Reasonable to contemplate RCT in asymptomatic or mildly symptomatic hyperleucocytosis of leukapheresis + chemotherapy versus chemotherapy alone in a specific disease e.g. AML

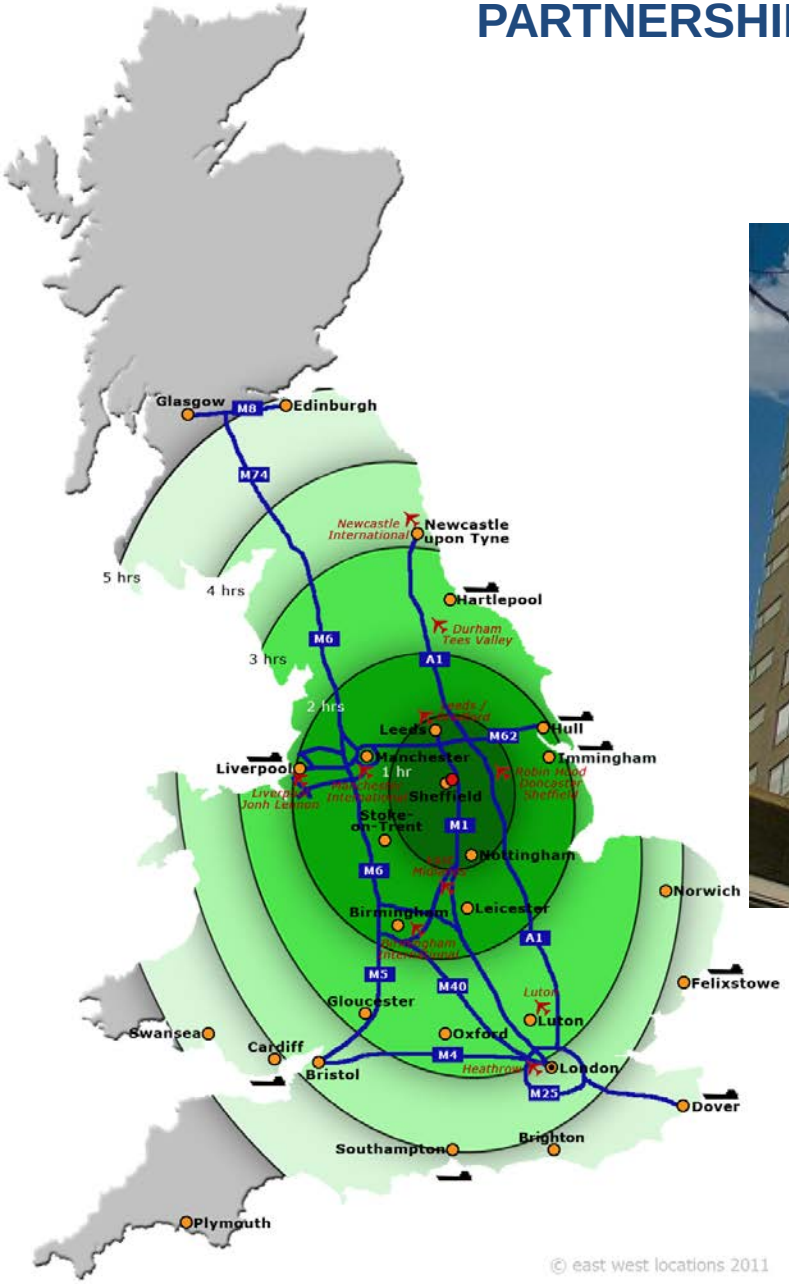
- ?Unethical to trial leucopheresis in patients with more established leucostasis

- Could NHSBT run this trial via satellite units?

Thank you from South Yorkshire

PARTNERSHIP

NHS Blood and Transplant



In aid of Anthony Nolan

ANTHONY NOLAN

BE A MATCH, SAVE A LIFE

The University Of Sheffield.