Early Good Evening Well come to all of you in this Sesation.

Title of the topics:

- Use of Arsenic Trioxide in Adult Severe aplastic anemia (AA).

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Objective of my presentation

- Investigate the efficacy of Arsenic trioxide
- in patient with refractory severe aplastic anaemia.

I would like to begin

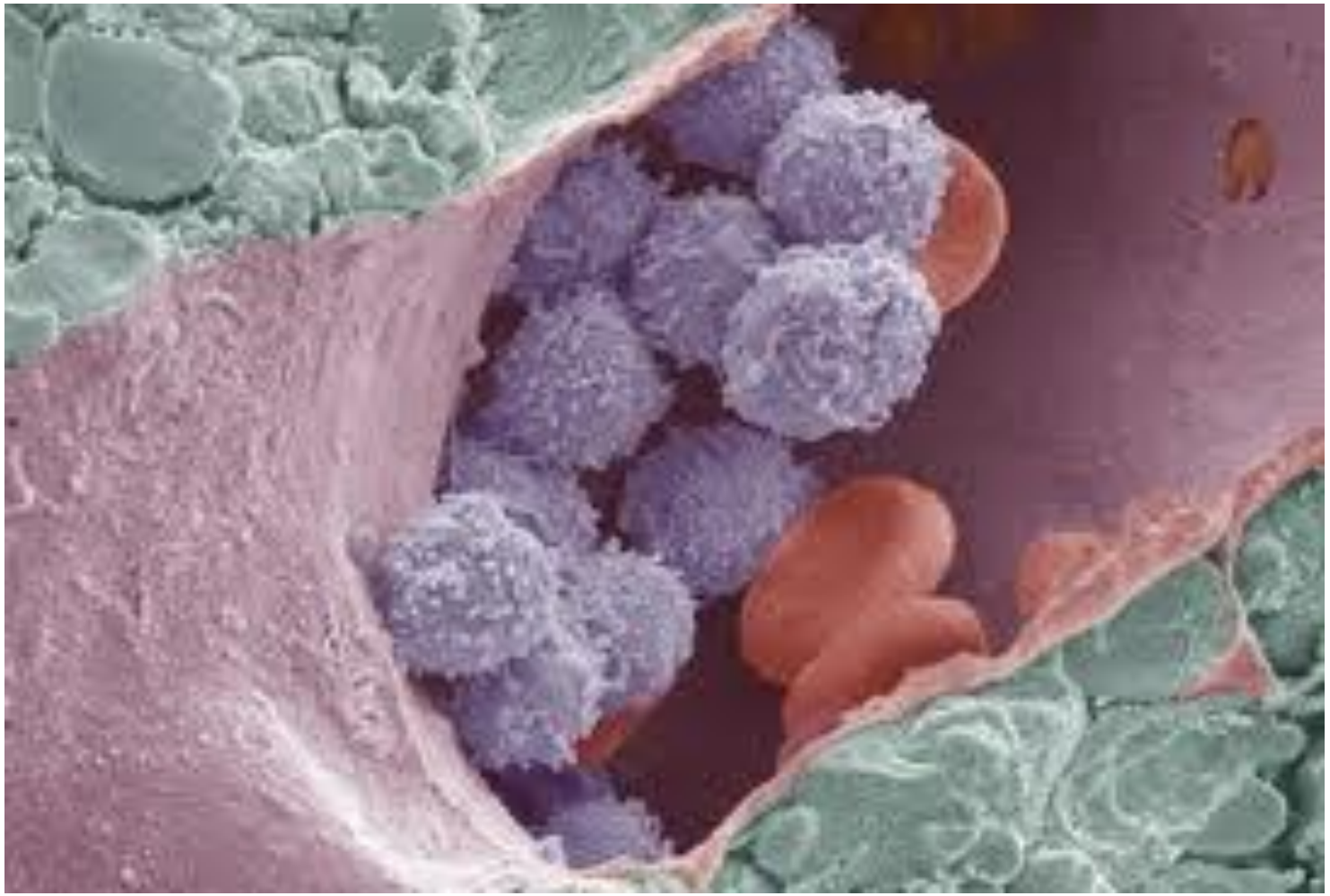
I have divided the talk into 03 Parts.

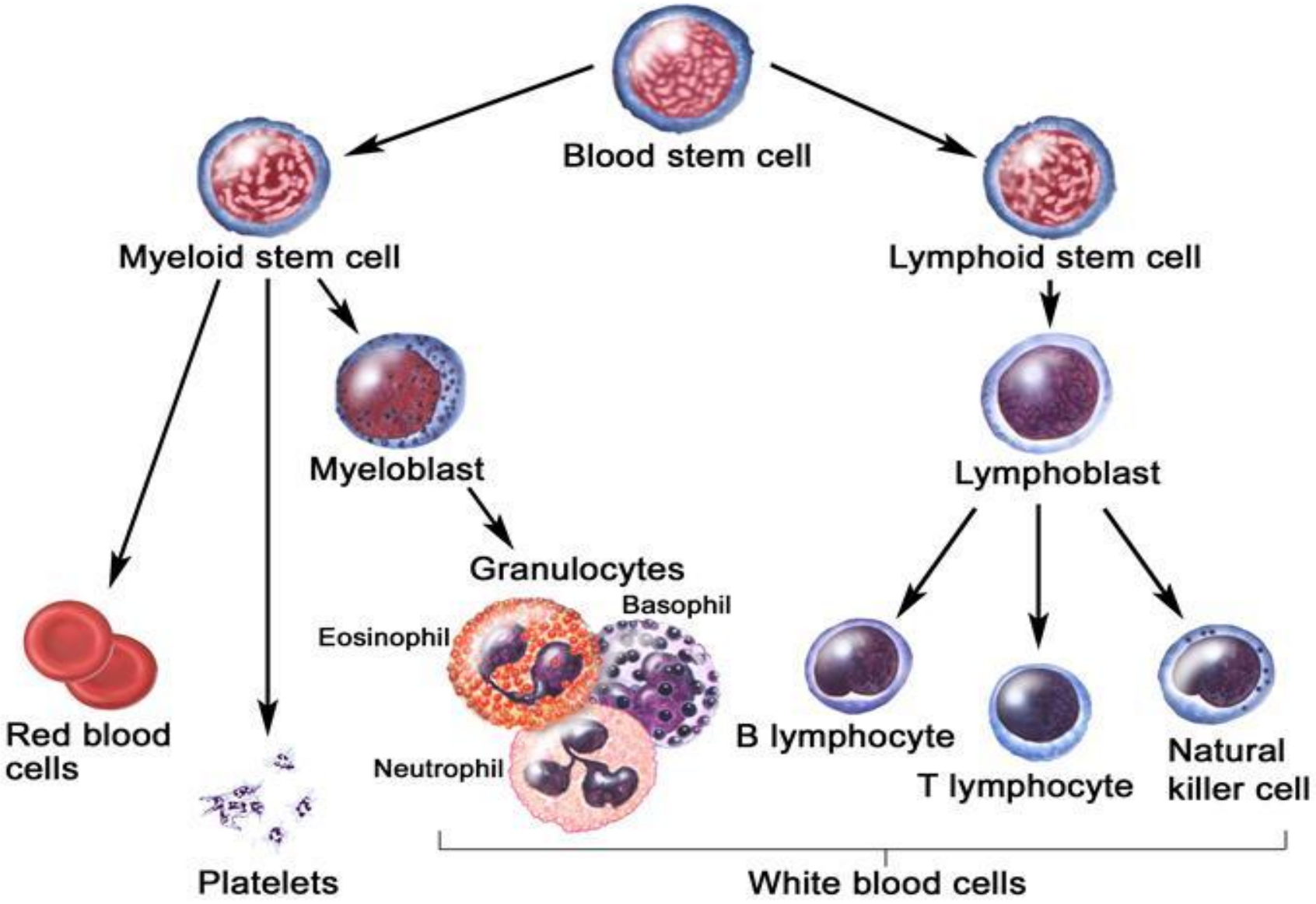
- Short overview on Haemopoiesis. and aplastic anaemia (AA).
- Current treatment of AA.
- Outcome of Arsenic trioxied (ATO).

Haemopoiesis:

All prepheral cell arise from common progenitor cells knows as pluripotent stem cells.

E/M Picture of Stem Cell





Aplastic anaemia (AA): is Characterised by

- peripheral pancytopenia.
- hypocellular bone marrow in the absence of an abnormal infiltrate.

Historical Background

The earliest case of aplastic anemia was described by Dr. Paul

Ehrlich in 1888. He described a young woman who died following

an abrupt illness that manifested as severe anemia, bleeding,

hyperpyrexia, with markedly hypocellular bone marrow.

The term *aplastic* anemia was first introduced in 1904 by Chauffard.

Types of Aplastic Anaemia.

- Primary :(a) Idiopathic
  (b) Congenital.

- Secondary : (a) Radiation
  (b) Drug
  (c) Chemical
  (d) Autoimmunity

Incidence and age distribution

In the West 2 per million per year.

Two to threefold higher incidence rate in Asia.

There is no data in our country.

Age Incidence: 15 to 25 yrs

There is a second smaller peak after 60 years

Aetiological agents

Aplastic anemia has been causally associated with many agents:

Drugs and chemical,

Radiation,

Benzene and enviromental toxin exposure,

Insecticides,

Viruses

Although most of the cases no etiologic agent can be identified.

AA. may be associated with other systemic autoimmune disorders

- Eosinophilic fasciitis
- Systemic lupus erythematosus (SLE),
- Sjögren syndrome
- Coeliac disease.
- Also pregnancy rarely associated with aplastic anaemia.

Pathogenesis

The exact mechanisms is not completely known
Haemopoietic failure can result from :

- Reduction in the number of stem cells.
- Defective stem cells.

- Defective haemopoietic microenvironment that is not able to sustain normal haemopoiesis.
- Autoimmunity.
- Cytotoxic T lymphocytes.
- Overproduction of interferon-γ and tumor necrosis factor (TNF).

Autoimmune etiology for the majority of patients in AA.

Cytotoxic T lymphocytes were found to mediate the destruction of haemopoietic stem cells in aplastic anemia.

These cytotoxic T cells are more conspicuous in the bone marrow of AA patients than in the peripheral blood

They overproduce interferon-γ and tumor necrosis factor (TNF).

TNF and interferon-γ are direct inhibitors of haemopoiesis.

Clinical features of AA.

- Symptoms of anaemia.
- Skin or mucosal haemorrhage (ecchymoses or petechiae), including buccal haemorrhages.
  visual disturbance due to retinal haemorrhage
- Infection, particularly sore throat or failure of minor infections to clear.
- There is no organomegaly and
  absence of infection.

Definition of disease severity of aplastic anaemia.

Severe AA

Bone marrow cellularity < 25%, or 25– 50% with < 30% residual haemopoietic cells

Two out of three of the following:

- Neutrophils < 0.5 × 10 9 /L
- Platelets < 20 × 10 9 /L
- Reticulocytes <20 x 10 9/L

Very severe AA:

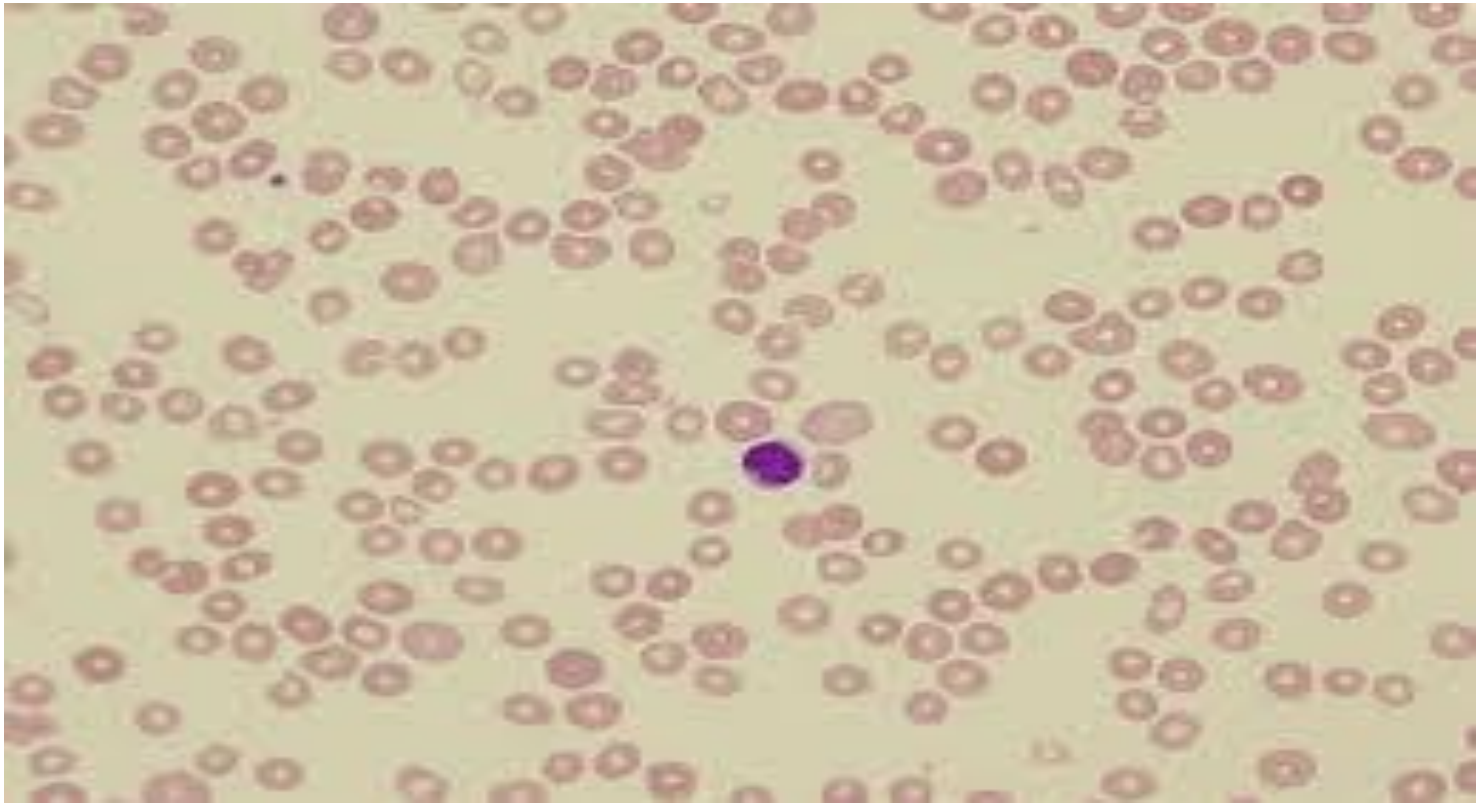
Like severe AA but neutrophils < 0.2 × 10 9 /L

Non - severe AA

Patients not fulfilling the criteria for severe or very severe AA

Laboratory Features

PBF **:** Pancytopenia.



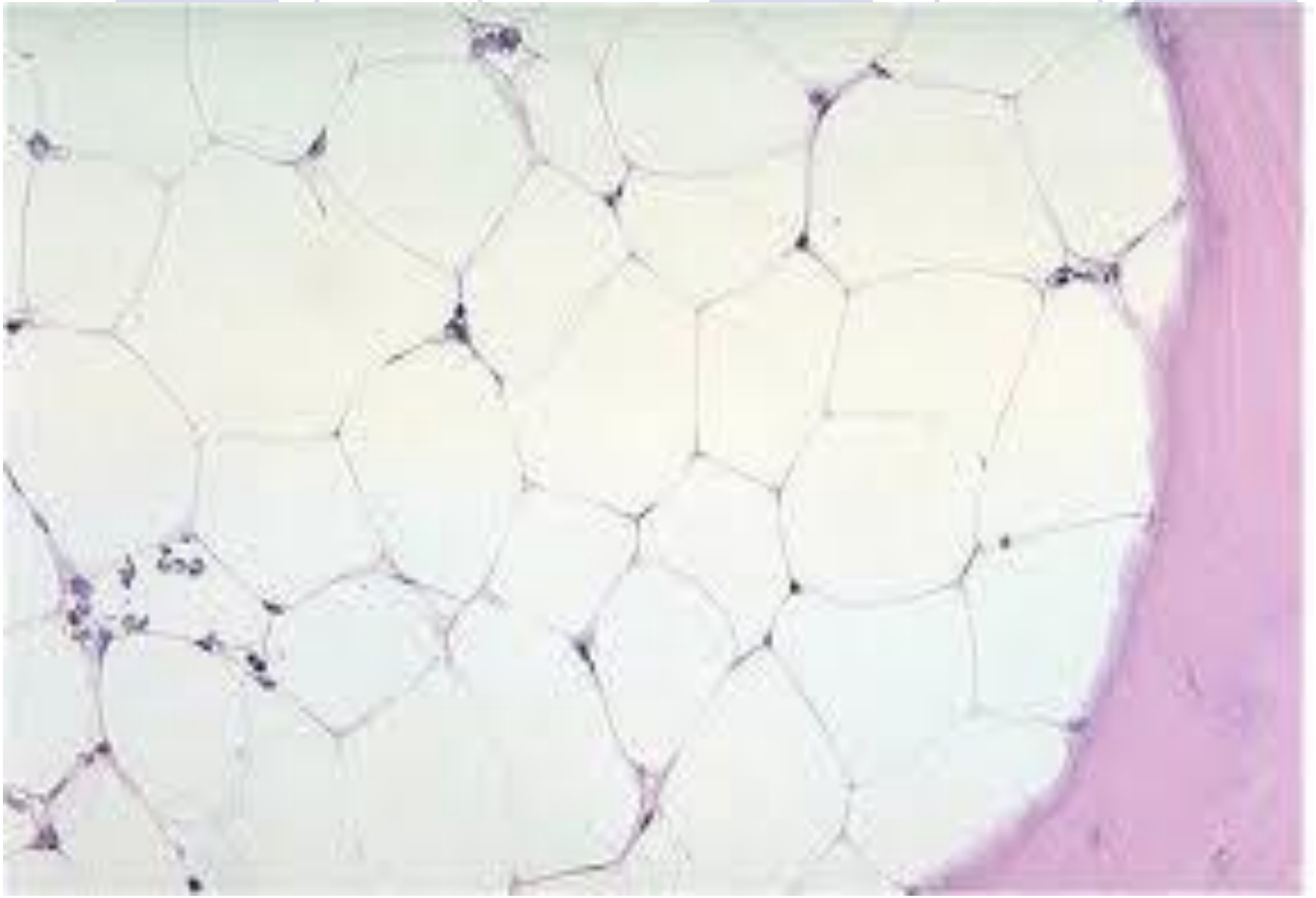
Bone Marrow **:** Hypocellular with prominent fat spaces and variable amounts of residual haemopoitic cells.

Erythropoiesis : is reduced with some some digree of dyserythropoiesis.

Granulopoieis **:** Reduced.

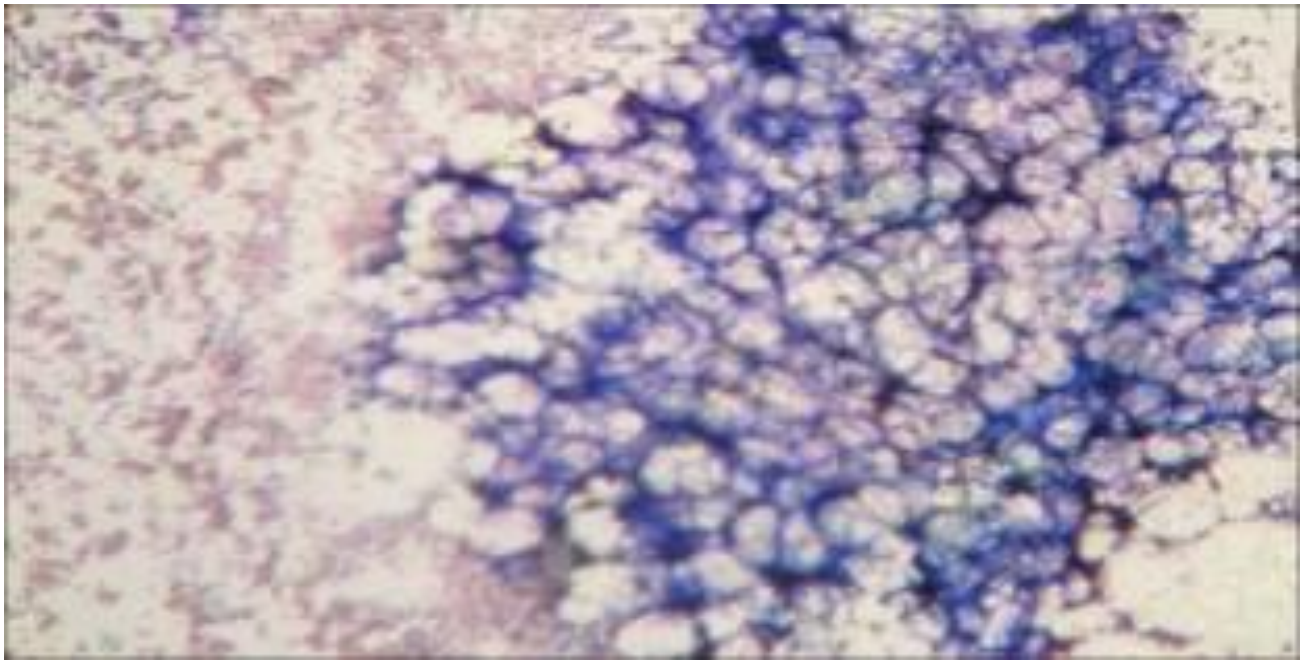
Megakaryocytes **:** Scanty or absent.

Lymphocytes **:** macrophages, plasma cells and mast cells appear prominent.



Trephine Biopsy : The trephine is needed to assess overall cellularity, the morphology of residual haemopoietic cells and to exclude an abnormal infiltrate.

The trephine is hypocellular throughout but is sometimes patchy, with hypocellular and cellular areas.



Differential diagnosis

The following disorders may sometimes present with pancytopenia and a hypocellular bone marrow.

- **Hypocellular MDS/AL**
- **Aleukaemic leukaemia**
- **Hairy cell leukaemia**
- **Lymphomas, either Hodgkin disease or non- Hodgkin lymphoma, and myelofibrosis.**
- **Mycobacterial infections, especially atypical infection.**
- **Anorexia nervosa or prolonged starvation**

Second Part of my talk

Current Treatment of Aplastic anaemia

Management

Supportive care :

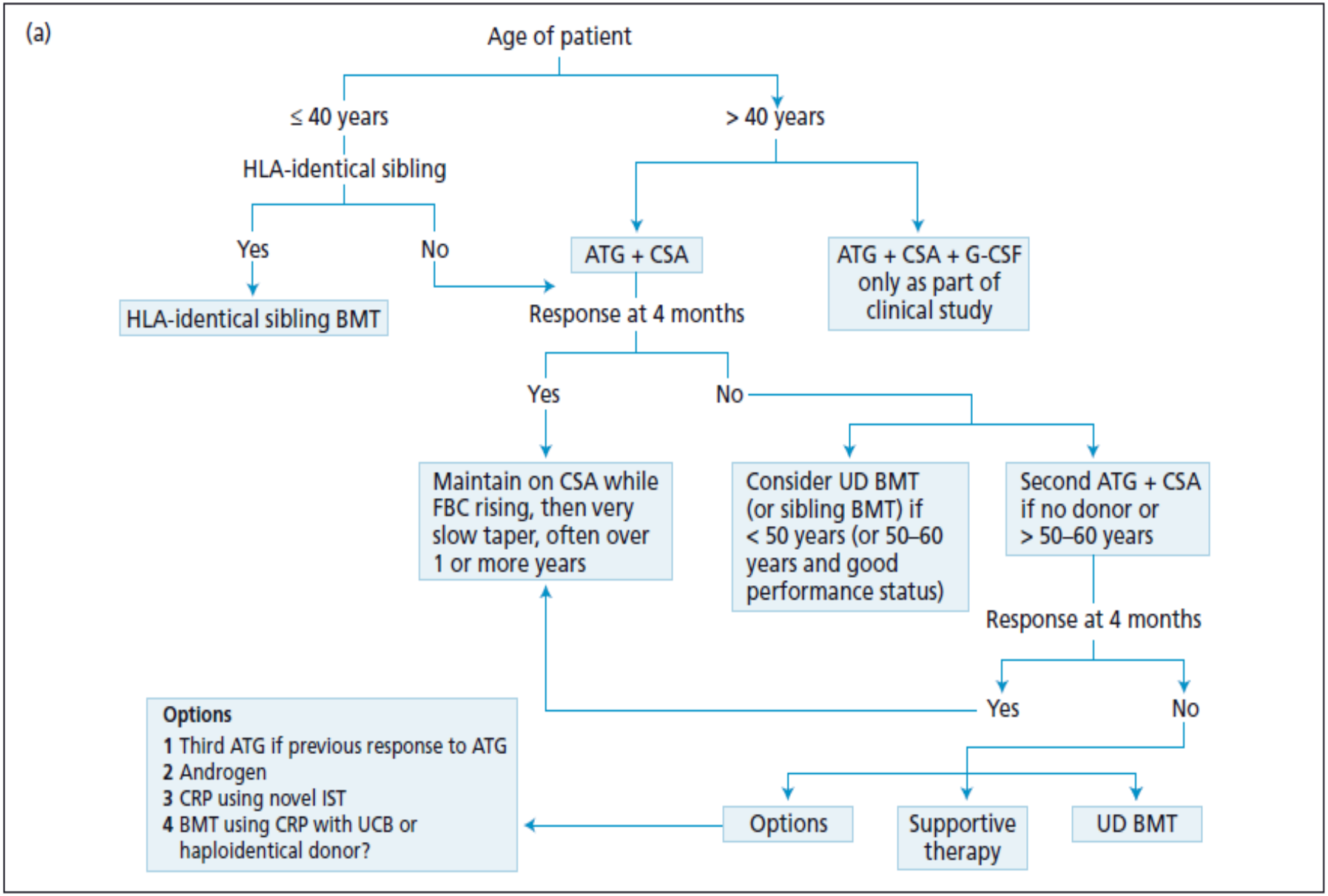
- Transfusions
- Antibiotics
- Iron Chelation

Definitive Treatment

Bone Marrow Transplantation (Allogenic HSCT) :

If the disease is very severe or severe disease.
If there is HLA match sibling donor.
If the patient is younger (<50 years).

Antithymocyte Globulin + Ciclosporin : If the patient age >50 years.
If there is no HLA match sibling donor.


(a)
Age of patient
≤ 40 years
> 40 years
HLA-identical sibling
Yes
No
HLA-identical sibling BMT
ATG + CSA
ATG + CSA + G-CSF only as part of clinical study
Response at 4 months
Yes
No
Maintain on CSA while FBC rising, then very slow taper, often over 1 or more years
Consider UD BMT (or sibling BMT) if < 50 years (or 50–60 years and good performance status)
Second ATG + CSA if no donor or > 50–60 years
Response at 4 months
Yes
No
Options
1 Third ATG if previous response to ATG
2 Androgen
3 CRP using novel IST
4 BMT using CRP with UCB or haploidentical donor?
Options
Supportive therapy
UD BMT

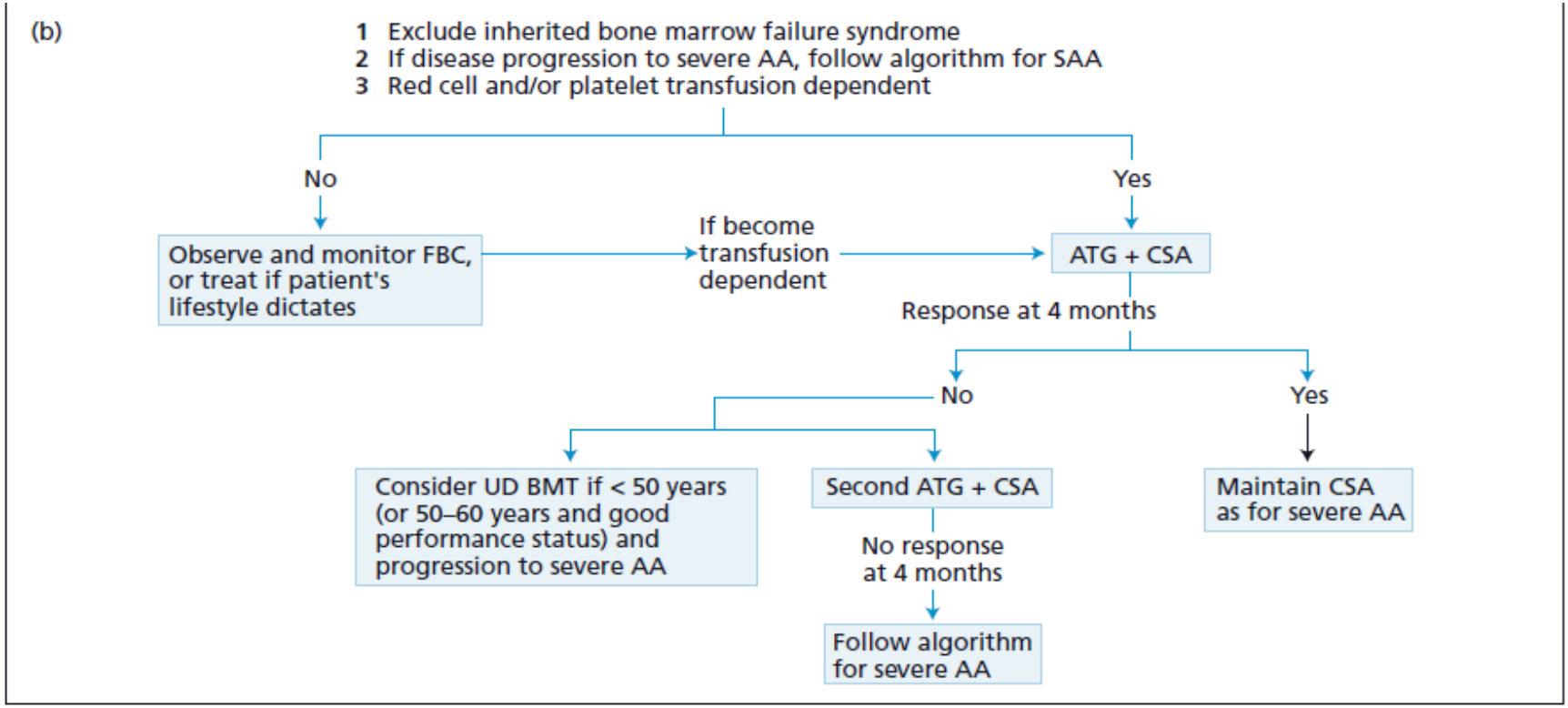
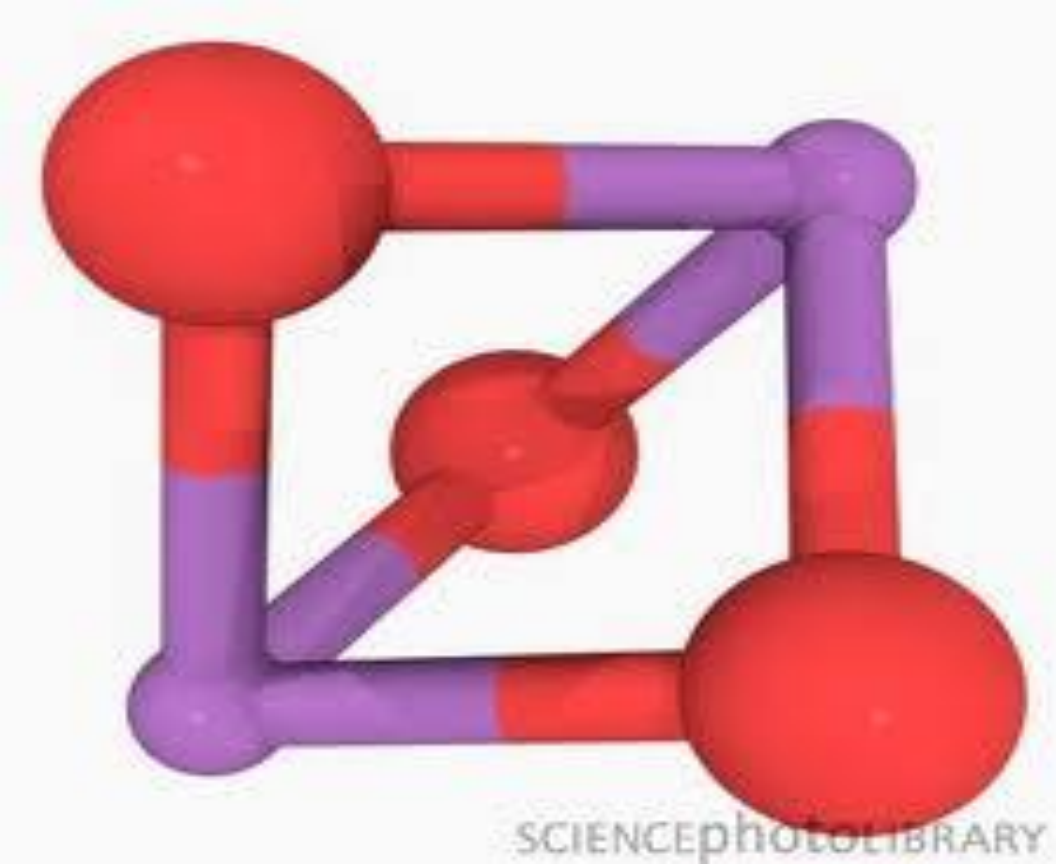


Figure 13.4 Algorithms for treatment of (a) severe acquired aplastic anaemia and (b) non-severe aplastic anaemia. AA, aplastic anaemia; ATG, antithymocyte globulin; BMT, bone marrow transplantation; CSA, ciclosporin; FBC, full blood count; IST, immunosuppressive therapy; UD, unrelated donor; HLA id sib BMT, HLA-identical sibling BMT; CRP, clinical research protocol; UCB, umbilical cord blood. (Modified from Marsh *et al.* (2009) *British Journal of Haematology* **147**: 43–70, with permission of Wiley Publishers.)

Last Part of my Presentation is a new

approach of treatment with arsenic trioxide plus ciclosporin in adults with severe aplastic anaemia shows improve outcome.

Arsenic trioxide is the inorganic compound with the formula As2O3.



Currently

About one-third of patients with aplastic anaemia are refractory to anti-thymocyte globulin (ATG).

Refuse to receive ATG/ciclosporin-based immunosuppressive regimens.

For such patients,a novel therapeutic alternative approach with arsenic trioxide (ATO) plus ciclosporin was investigated in this study.

No. of patient: 10 adults with severe aplastic anaemia (SAA). were enrolled between April 2011 to December 2012.

ATO was administered at a dose of 0.15 mg/kg I/V daily for 5 days in a wk for 8 wks.

Ciclosporin (5 mg/kg orally daily) was started from day one for 6 months.

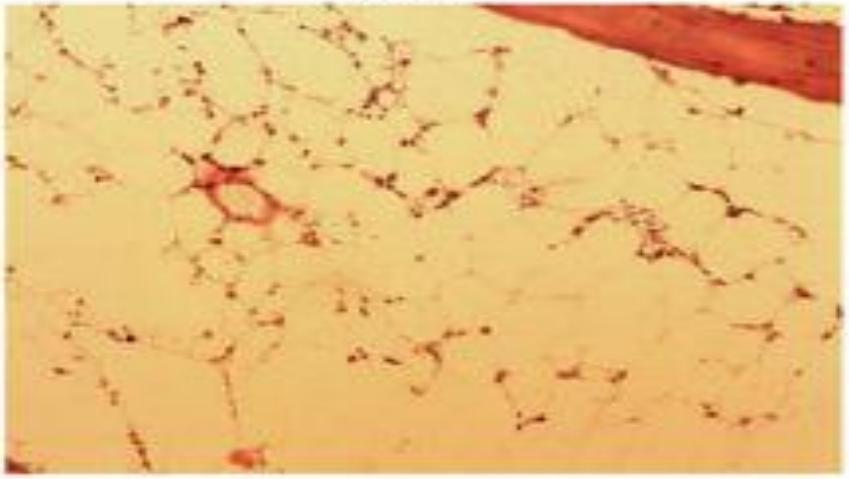
The dose was adjusted to achieve a whole blood trough level of 100–200 ng/ml.

Table I. Patients' characteristics before and after arsenic trioxide plus ciclosporin treatment.

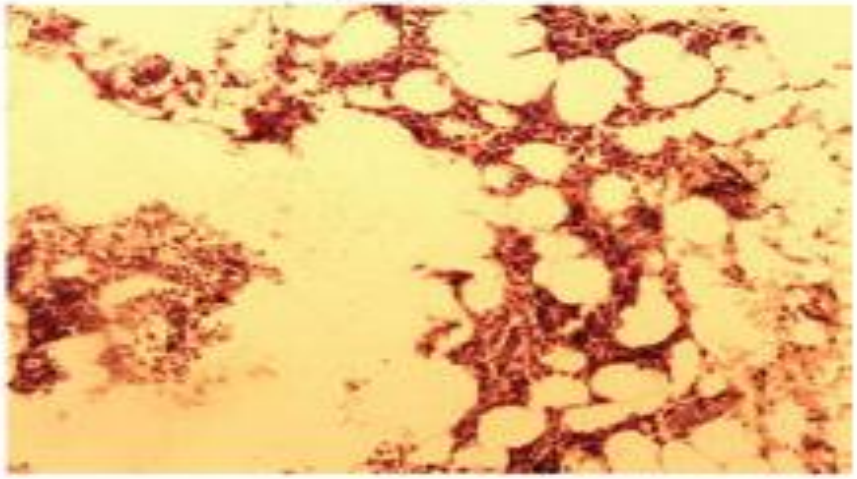
Patient	Age (years)/ gender	Platelet count ($\times 10^9$/l)		Haemoglobin (g/l)		ANC ($\times 10^9$/l)		Time to initial Response (days)	Time to maximum response (days)	Final response	Present status
		Before therapy	After maximum response	Before therapy	After maximum response	Before therapy	After maximum response				
1	21/M	9	124	50	109	0·1	2·1	38	51	CR	CR and well 62 months
2	36/F	12	151	51	116	0·2	1·8	46	69	CR	CR and well 53 months
3	43/M	15	59	47	84	0·1	0·7	40	61	PR	PR and well 50 months
4	39/F	11	127	59	126	0·2	1·9	43	101	CR	CR and well 46 months
5	27/M	6	118	57	122	0·3	1·8	43	94	CR	CR and well 41 months
6	23/M	9	140	61	110	0·2	1·7	44	86	CR	CR and well 40·6 months
7	35/F	13	76	60	87	0·2	0·8	41	73	PR	PR and well 40·1 months
8	41/M	13	109	61	134	0·4	1·9	41	83	CR	CR and well 39 months
9	39/F	16	128	59	125	0·3	1·8	39	53	CR	CR and well 37·3 months
10	19/M	10	119	58	123	0·1	2·0	41	91	CR	CR and well 36 months

M, male; F, female; ANC, absolute neutrophil count; CR, complete response; PR, partial response.

Baseline

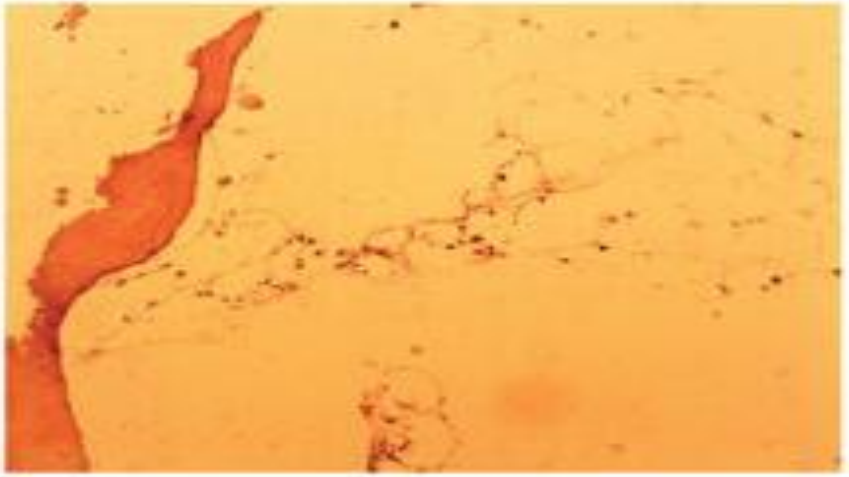


8 weeks

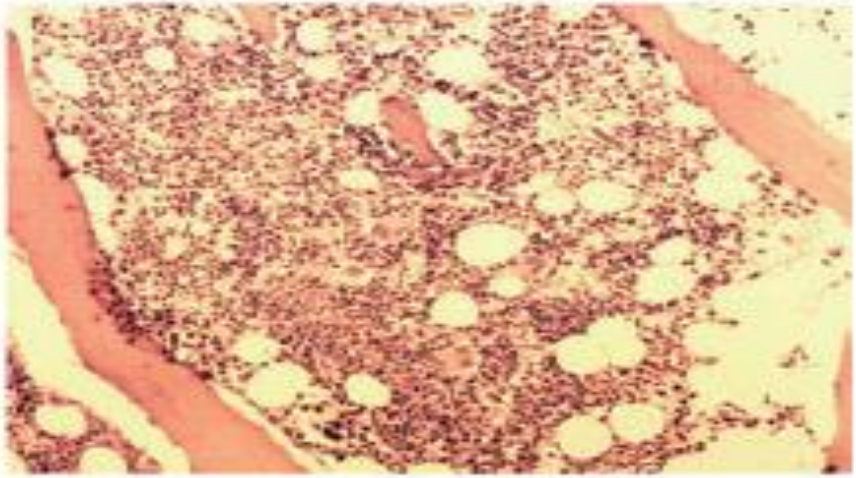


Patient 4

Baseline



12 weeks



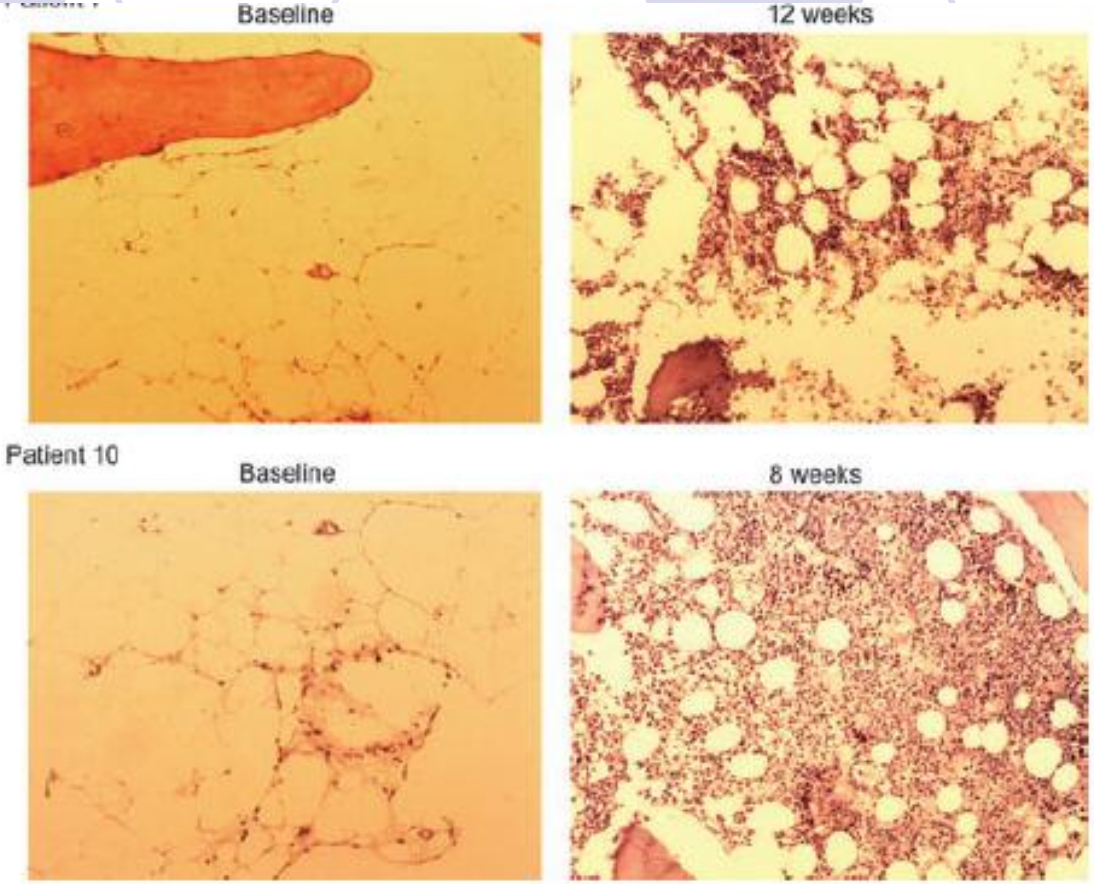


Fig 1. Antagonizing marrow adipogenesis by arsenic trioxide enhances haematopoietic recovery in 10 adults with aplastic anaemia. Bone marrow–biopsy specimens stained by Haematoxylin and Eosin (original magnification ×100) are shown for four patients who had a response to arsenic trioxide and were followed for at least 8 weeks after protocol initiation.

approach for patients with aplastic anaemia. A total of 10 con-

All patients with SAA were administered ATO plus ciclo-

Response was defined as the absence of recent transfusion.

Complete response (CR)(i) haemoglobin >100 g/l;
(ii) absolute neutrophil count (ANC) >1 x 109/l;
(iii) platelet count >100 x 109/l.

Partial response (PR): (i) transfusion independence
(ii) haemoglobin80g/l
(iii) ANC >0.5 x 109/l,
(iv) platelet count >30 x 109/l.

Transfusion dependence was taken as evidence of no response. Relapse was indicated by the requirement for blood transfusion after having been independent from transfusions for at least 3 months.

The overall response rate at 8 weeks was 100% (10/10);
30% (3/10) CR
70% (7/10) PR.

The median time to initial response was 41 d (range, 38–46 d).

Seven pts with a PR continued to receive a 2nd course of ATO and have clinically significant improvements in blood counts.

05 of them eventually met response criteria for CR at 17 weeks.

Serial bone marrow biopsies showed haemopoietic recovery accompanied by a decrease in adipocyte number.

To date, no patient has relapsed and shown evidence of clonal evolution or cytogenetic abnormalities

ATO-related toxicities (no of patient 10):

Skin reactions(rash, n = 1),
Gastrointestinal reactions (nausea, n = 1),
Liver dysfunction (n = 1)
Facial oedema (n = 2).

All the side effects were modest and responded to symptomatic treatment.
No patient discontinued therapy because of ATO related toxicities.

SAA is characterized by a reduced number of haemopoietic cells and adipocyte replacement in the bone marrow.

Studies suggest that bone marrow adipocytes are predominantly negative regulators of the bone marrow microenvironment.

Moreover adipocytes secrete tumour necrosis factor alpha and neuropillin-1, which can inhibit progenitor activity or impair haemopoietic proliferation.

Inaddition data show that ablation of the bone marrow adipocyte compartment can induce osteogenesis which promotes a more supportive environment for haemopoietic reconstitution.

Adipocytes and osteoblasts originate from mesenchymal stem cells (MSCs) within the bone marrow, where both display an inverse or reciprocal relationship and that ATO could regulate the adipogenic and osteogenic differentiation of MSCs by significantly inhibiting adipogenic differentiation and enhancing MSC osteogenic differentiation.

Conclusion:

ATO might serve as an adjuvant to haemopoietic recovery for patients with SAA in immunosuppressive therapy.
In the study, all patients achieved clinically significant responses to ATO plus ciclosporin.

Therefore, treatment with ATO plus ciclosporin may be a novel therapeutic approach in patients with aplastic anaemia.

References

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thank you