Ministry of Defence

Synopsis of Causation

Myelodysplastic Syndromes and Acute Myeloid Leukaemia

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. **Myelodysplastic syndromes** (MDS) are a group of disorders with common features on microscopic examination of bone marrow, but with diverse biological abnormalities and highly variable prognosis. The bone marrow production of blood is impaired by the outgrowth of abnormal cells (malignant "clonal" cells) which cannot mature, and die prematurely in the bone marrow. This results in low blood counts. In addition, the different subtypes have a variable rate of transformation to acute myeloid leukaemia (see 1.2). Several subtypes are defined by the World Health Organisation (WHO)[1] and previously by the French-American-British (FAB) classification.

1.2. **Acute myeloid leukaemias** (AML) are also a group of disorders with variable outcome. Bone marrow cells become malignant and fail to mature into healthy blood cells; they also fail to undergo normal cell death and so accumulate in the bone marrow. Leukaemia cells expand at the expense of healthy cells, causing low blood counts. Leukaemia cells often spill over into the peripheral bloodstream causing a high white blood cell count. The WHO classification defines subtypes by both their associated genetic changes (chromosome abnormalities/karyotype) and their appearance on microscopy (morphology).

2. Clinical Features

2.1. Most patients with MDS will be anaemic at some stage; 40% at diagnosis and 80% during the course of their disease. Symptoms of anaemia include fatigue, and breathlessness (dyspnoea), particularly on exertion. Severe anaemia can cause heart failure. Most patients will also have low numbers of neutrophils, which play a defensive role in dealing with infections, and platelets, which are necessary for normal clotting of the blood. Thus, recurrent infections are frequent, particularly affecting the chest, skin, mouth and urine, and if severe causing septicaemia. Infection is the major cause of death in 20 to 35 percent of patients.[2] Excessive bruising and bleeding are also frequent, predominantly from skin, nose and mouth, and occasionally more severe internal bleeding may occur.

2.2. Patients with AML also usually present with symptoms of low blood counts as in MDS. Infection complicated by septicaemia is more common as a presenting feature. Specific subtypes of AML have distinctive clinical features, including a major bleeding tendency in acute promyelocytic leukaemia (APL or FAB classification M3) and gum swelling in acute monocytic leukaemia (FAB M5).

3. Aetiology

3.1. **Myelodysplastic syndromes (MDS).** For the vast majority of patients with MDS, the aetiology remains unknown. Given that the biology of the group of disorders classified together as MDS is very different, it is clear that the aetiology of the subtypes of MDS will similarly differ.

3.1.1. **Age**. The incidence of MDS increases with age, reaching 30 per 100,000 population over 70 years of age. The relationship between an "ageing" bone marrow and the increasing likelihood of developing MDS is unknown.

3.1.2. **Genetic Factors.** Although families with several affected members are described, this is vanishingly rare. There is no evidence for a strong inherited component to the disease although the study of interactions between environmental factors and weak genetic predisposition (polymorphisms) to develop bone marrow damage is in its infancy.

3.1.3. **Previous cytotoxic chemotherapy.** This is the only confirmed causative risk factor for MDS. Although a rare complication of chemotherapy, exposure to alkylating agents can unequivocally lead to the development of MDS, which usually develops within 8 years of exposure. The subtype of MDS in this context is usually a high-risk MDS, with an abnormal, often complex karyotype and bone marrow scarring (fibrosis). This type of MDS is often referred to as therapy-related MDS (t-MDS). Refractory anaemia with ring sideroblasts and chronic myelomonocytic leukaemia subtypes of MDS are rarely seen as t-MDS.[3]

3.1.4. **Tobacco smoke exposure.** Most studies indicate a weak but consistent association between cigarette smoking and MDS.[4] The magnitude of increased risk is approximately 1.5. Although this association is often attributed to the benzene component, there are more than 200 toxic chemicals in tobacco smoke which could be responsible.

3.1.5. **Radiation.** MDS cases have been reported in people exposed to radiation for treatment of diseases such as ankylosing spondylitis,[5] or following exposure to the A-bomb in Hiroshima and Nagasaki.[6] Some of these cases occurred up to 40 years after exposure and thus it is not possible to quantify the precise association between the development of MDS and exposure to radiation. The incidence of MDS does not appear to be increased following local radiotherapy for lymphoma, but is probably increased following total body irradiation exposure at autologous stem cell transplant.[7] The evidence for an association between environmental/occupational radiation exposure and MDS is weak, with inconsistency between case-control epidemiology studies.[8,9] There is no evidence for an association between MDS and ultraviolet or electromagnetic radiation exposure but this has not been systematically studied.

3.1.6. **Benzene.** Exposure to high concentrations of benzene causes bone marrow damage, usually aplastic anaemia, which occasionally leads to subsequent MDS.[10] However the exposures described in the literature were at considerably higher concentrations than are now encountered in the Western workplace.

3.1.7. **Miscellaneous.** Several case-control studies have reported weak associations between MDS and exposure to a variety of environmental toxins, or allied to specific occupations. There is a lack of consistency between exposures reported in different studies, except perhaps for exposure to solvents and pesticides. However, the numbers studied in all reports are relatively small, and all cases of MDS have been considered together when it is now clear that many of the different subtypes should be studied individually. This is far removed from demonstrating cause and effect for these occupation-related environmental toxins. There is limited evidence that hair dye use[11] and excess alcohol consumption[12] increase the risk of MDS. There is no evidence implicating infection as a cause of MDS.

3.2. **Acute myeloid leukaemia (AML).** As for MDS, for the vast majority of AML patients, the aetiology remains unknown. Also as for MDS, the biology of the different subtypes of AML varies and the aetiology of these subtypes will clearly differ. Most studies referred to below group all types of AML together, thereby limiting the conclusions that can be drawn. The toxic insults known to cause MDS are also implicated in the aetiology of AML and together they are often regarded as a continuum of disorders, progressing from MDS to AML.

3.2.1. **Genetic factors.** Familial cases of AML are rare. Some inherited constitutional disorders predispose individuals to cancer, including AML. However, there are no genes yet identified that strongly predict the development of AML. A number of genes may weakly influence an individual's susceptibility to develop AML but this area of research is in its infancy.

3.2.2. **Age.** The incidence of AML increases with age, and the distribution of subtypes of AML changes with age. Patients with "good risk" chromosome changes [chromosome translocations t(15;17), t(8;21) and inv(16)] are younger and those with "poor risk" chromosome abnormalities (usually involving complex chromosomal abnormalities) are generally older. This reflects the biology of these diseases in relation to age, and does not simply demonstrate that younger patients can tolerate chemotherapy better than older, although an element of this is true. Younger patients with "poor risk" disease still fare relatively badly.

3.2.3. **Previous cytotoxic chemotherapy.** AML following exposure to chemotherapeutic alkylating agents is similar to that for t-MDS above. In addition, AML can follow exposure to another group of chemotherapy drugs, the epipodophyllotoxins, with a shorter time to onset after exposure (usually within 1 to 2 years). Finally, acute promyelocytic leukaemia (APL, M3 AML) is now recognised following exposure to anthracycline drugs, particularly mitoxantrone.

3.2.4. **Tobacco smoke exposure.** As for MDS, exposure to tobacco smoke is a consistent but weak risk factor for the development of AML.[13]

3.2.5. **Radiation.** There is clear evidence from atomic bomb survivors that relatively high dose exposure to ionising radiation can cause AML, with an increased risk which peaked at 10 years after exposure, and persisted for approximately 15 years after exposure.[14] The data for incidence of AML after nuclear testing in the Pacific are inconsistent.[15,16] Occupational exposure to high doses of radiation also increases the risk of AML, but these are historical cohorts

(usually before 1940) and such a risk no longer appears to be identifiable.[17,18] **Radiotherapy** for malignant and non-malignant conditions can also increase the risk of subsequent AML, but is no longer offered for non-malignant conditions. Local radiotherapy for cancer is probably not a significant risk factor for AML development when used as the only treatment. Radiotherapy in combination with chemotherapy, particularly when radiotherapy is more generalised such as in autologous stem cell transplantation may be a weak risk factor for the subsequent development of AML.[7] There is no evidence for an association between AML and ultraviolet or electromagnetic radiation exposure but this has not been systematically studied.

3.2.6. **Benzene.** The data for occupational exposure to high concentrations of benzene indicate a cause and effect for the development of AML.[19] As for MDS, these exposures are now historical, with strict exposure limits now imposed upon modern Western industry. Current maximum exposure limits in the UK are 1 ppm averaged over an 8 hour period.[20] The data for the relationship between exposure to low doses of benzene and the development of AML are contentious, and usually rely on models of linear extrapolation from high-dose exposure studies. Environmental exposure to benzene is predominantly in tobacco smoke and unleaded petrol. Although tobacco smoke exposure is a weak risk factor for AML, it does contain hundreds of carcinogens. No consistent increased risk of developing AML has been identified for car users or petrol station employees.

3.2.7. **Miscellaneous.** There is no strong evidence implicating **infection** as a cause of AML. Evidence exists for a possible weak association between AML and selected **occupations**, including painters,[21] embalmers,[22] workers in the meat[23] and rubber manufacturing[24] industries and agricultural workers (less consistent).[25] Although a number of **chemicals**, such as benzene, organic solvents, butadiene, and pesticides are considered potentially causative, there is no epidemiological evidence to convincingly implicate any of these. As in MDS, hair dye usage and alcohol intake are recreational agents also weakly implicated as potentially causative for AML.

4. Prognosis

4.1. **MDS** The term MDS encompasses a group of different diseases and the prognosis is highly variable.

4.1.1. **Predicting prognosis – scoring systems**. Several scoring systems have been devised to try to predict conjectured survival, the latest of which is the International Prognostic Scoring System (IPSS).[26] Using three parameters, some idea of prognosis can be obtained but the confidence intervals are large. The median survival (years) without treatment for the four prognostic groups is Low – 5.7, Intermediate-1 – 3.5, Intermediate-2 – 1.2, High – 0.4. Patients less than 60 years with Low and Int-1 disease have longer survival than those aged more than 60 years. For Intermediate-2 and High risk disease, age has no impact on survival. Most patients die from the complications of low blood counts (infection/bleeding). Transformation to AML is more frequent in the higher risk groups and the median time (years) for 25% patients to transform to AML from each risk group is Low – 9.4, Intermediate-1 – 3.3, Intermediate-2 – 1.1, High – 0.2.

4.1.2. If the IPSS score cannot or has not been calculated for an MDS patient, the FAB subtype offers a rough survival estimate with the largest study indicating the following survival times (months): Refractory anaemia (RA) – 37, Refractory anaemia with ring sideroblasts (RARS) – 50, Refractory anaemia with excess blasts (RAEB) – 12, Refractory anaemia with excess blasts in transformation (RAEB-t) – 5, chronic myelomonocytic leukaemia (CMML) – 19.[27] Within the RA subgroup, the WHO subtypes RA, and 5q- syndrome have a very good prognosis, as does the WHO subtype RARS (note – this has changed from the FAB subtype RARS).

4.2 **AML** As for MDS, the prognosis for AML is highly dependent upon the subtype. Age is a very strong predictor of survival in AML, predominantly due to the different subtypes of AML seen at different ages. Nevertheless, survival is more dependent upon the biological subtype (usually defined by the chromosome change or karyotype), than age alone. Patients with a complex karyotype at any age have a very poor prognosis with only 5 to 10 percent alive after 5 years.

4.2.1 **AML in younger patients**. The cure rate for all patients less than 60 years old is approximately 45%.[28] A high cure rate (more than 60%) is now possible for the three subtypes most commonly seen in younger patients, which are all characterised by well-defined chromosome abnormalities; namely APL with t(15;17), FAB M4 with eosinophilia (M4Eo) with inv(16), and FAB M2 with t(8;21).[29] Cure rates for APL are now greater than 80%.[30] These subtypes are less common in older patients and the prognosis for these subtypes in older patients is considerably poorer.

4.2.2 **AML in older patients**. For patients aged between 60 and 75 years fit enough for intensive chemotherapy treatment, cure rates of between 20 and 25% can be expected. For patients not fit for intensive chemotherapy, survival is very poor with only 5% alive at 2 years.

5. Summary

5.1 **MDS** is a group of disorders which share some overlapping features but also show significant individual differences, making it very likely that different subtypes have a different cause. Most epidemiological studies have grouped all MDS types together. The only certain causative agents for MDS are previous cytotoxic chemotherapy with alkylating agents, and exposure to high doses of ionising radiation and benzene (neither of which now occur in the Western world). The prognosis of different types of MDS varies greatly, and active treatment is available only for the minority of patients, largely because this is a disease of older people.

5.2 **AML** is also a disparate group of disorders, which is being increasingly defined by the genetic make up of the tumour types. The known and suspected causes of AML are largely as for MDS, but it is equally likely that different types of AML have very different causes. Epidemiology studies have also historically grouped all types of AML together. The prognosis of different types of AML also varies greatly, with high cure rates for some types, which are well defined by genetic abnormalities and occur in younger adults. At the opposite end of the spectrum, older patients fare worse with chemotherapy, although cure is still possible for a minority.

6. Related Synopses

Chronic Lymphoproliferative Disorders
Chronic Myeloid Leukaemia
Non-Hodgkin's Lymphoma
Polycythaemia

7. Glossary

aetiology	The study of the causes; for example, of a disorder.
alkylating agents	A family of chemotherapeutic drugs used to treat a variety of cancers.
anaemia	The condition of having less than the normal number of red blood cells or less than the normal quantity of haemoglobin in the blood. The oxygen-carrying capacity of the blood is, therefore, decreased.
ankylosing spondylitis	A polyarthritis involving the spine, which is characterised by progressive, painful stiffening of the joints and ligaments.
anthracycline	A member of a family of chemotherapeutic drugs used to treat cancer.
aplastic anaemia	Anaemia due to failure of the bone marrow to produce blood cells, including red and white blood cells as well as platelets.
autologous stem cell transplant	This is a procedure to treat blood cancers where healthy bone marrow or blood is sampled (harvested) and then infused back into the same patient after a large dose of chemotherapy and/or radiotherapy.
cytotoxic chemotherapy	Chemotherapy that is toxic to/kills cells.
dyspnoea	Breathlessness.
eosinophilia	An increase in the number of eosinophils in the blood.
epipodophyllotoxins	A family of chemotherapeutic drugs used to treat cancer.
fibrosis	The formation of excessive fibrous tissue, as in a reparative or reactive process.

“good risk” chromosome abnormalities	Chromosome translocations involving t(15;17), t(8;21) and inv(16).
karyotype/ chromosome abnormalities	The characterisation of the chromosomal complement of an individual or species, including number, form and size of the chromosomes.
median	The middle or centre.
mitoxantrone	An anthracycline drug.
morphology	Literally, the study of form. The study of structure. Also, the form itself, as of an organ or part of the body.
neutrophil	A type of white blood cell, specifically a form of granulocyte, filled with neutrally-staining granules, tiny sacs of enzymes that help the cell to kill and digest micro-organisms it has engulfed by phagocytosis.
platelet	An irregular, disc-shaped element in the blood that assists in blood clotting. During normal blood clotting, the platelets clump together (aggregate). Although platelets are often classed as blood cells, they are actually fragments of large bone marrow cells called megakaryocytes.
polymorphism	Variation within DNA (sequence) occurring within a species, and responsible for some of the differences between individuals.
“poor risk” chromosomes	Chromosome abnormalities, usually involving complex chromosomal changes.
prognosis	The expected course of a disease. Also, the patient's chance of recovery. The prognosis predicts the outcome of a disease and therefore the future for the patient.
radiotherapy	The treatment of disease with ionising radiation. Also called radiation therapy.

refractory anaemia	One of the groups of MDS categories usually associated with a better prognosis.
septicaemia	Invasion of the bloodstream by virulent micro-organisms from a focus of infection.

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