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REVIEW

Independent prognostic variables in acute myeloid leukaemia

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ABSTRACT

Acute myeloid leukaemia (AML) is one of the most common haematological malignancies and is increasing in frequency due to an ageing population. Whilst remission will be achieved in up to 80% of those receiving intensive chemotherapy, the main variables precluding cure are the treatment-related mortality and relapse rates. Decisions on intensification, de-escalation and allografting rely on the ability to divide an apparently homogeneous group according to risk. A wide range of clinical, cytogenetic and molecular variables may be used to inform this task. Cytogenetic and molecular characterisation has already identified subgroups, such as acute promyelocytic leukaemia (APL) with t(15;17)/*PML-RARA* and AML with *FLT3* mutation for which targeted therapies are available, and further molecularly defined groups who may be potential candidates for this approach are likely to be identified in the future. This review examines the range of established clinical and diagnostic parameters that should be used in assessing prognosis for a patient with AML and looks ahead to an expanding repertoire of potential variables that are currently under evaluation.

1. Introduction

Acute myeloid leukaemia (AML) is being revealed as an increasingly heterogeneous entity as the molecular aberrations underlying it are defined. Such information is fundamental in assessment of the chances of durable treatment response. Morphological complete remission (CR) is now achieved in the majority of patients with current chemotherapeutic regimens, so the main determinants of prognosis are therefore those variables that influence treatment-related death or relapse risk. Such information allows decisions on intensification and de-escalation of therapy, as well as decisions on the appropriateness of an allograft procedure in first remission with its consequent morbidity, mortality and financial costs. There is also an expanding portfolio of novel agents that have activity in AML. Cytogenetic and molecular characterisation has already identified subgroups of AML that benefit from molecularly targeted therapies, such as all *trans* retinoic acid (ATRA) and arsenic trioxide (ATO) in PML-RARA + acute promyelocytic leukaemia (APL) or inhibitors of the Fms like Tyrosine kinase 3 (FLT3) in AML with FLT3 mutation, and further molecularly defined groups who are potential candidates for this approach are likely to be identified in the future.

In counselling an individual patient, account needs to be taken of an increasing and rather bewildering array of clinical and biological variables. These include a range of well established prognostic factors as well as a variety of laboratory and molecular markers that have yet to find their place in routine risk stratification.

2. Established clinical variables

2.1. Age and performance status

Biological age is a highly significant prognostic variable adversely affecting both attainment of remission and relapse risk (Fig. 1). It has been repeatedly demonstrated that prognosis worsens with increasing age, both in terms of response and overall survival (OS).[1,2] This reflects concurrent co-morbidities and altered drug handling in addition to different disease biology with higher frequencies of adverse cytogenetics (Fig. 2), multidrug resistance protein (MDR-1) positivity, prior myelodysplasia (MDS) and a stem cell phenotype.[1,3] Older patients tolerate the complications of chemotherapy poorly with a significant risk of death during induction, mainly related to sepsis. For those patients less than 60 years, CR rates of 85% and 5-year survival rates of 38% have been observed.[4] For selected good risk patients over 60 years of age, with *de novo* disease and MDR-1 negativity, CR rates can approach 75% although, among all older patients treated with intensive chemotherapy, the Leukaemia Research Fund AML14 study gave response rates of 62% with a 5-year survival of 12%.[5] However at present it is unclear whether these prognostic variables are predictive in identifying those for whom palliative or experimental treatment approaches would be more appropriate.[6]

Poor performance status at diagnosis is further seen to adversely affect prognosis. Comorbidity index scores are predictive of early

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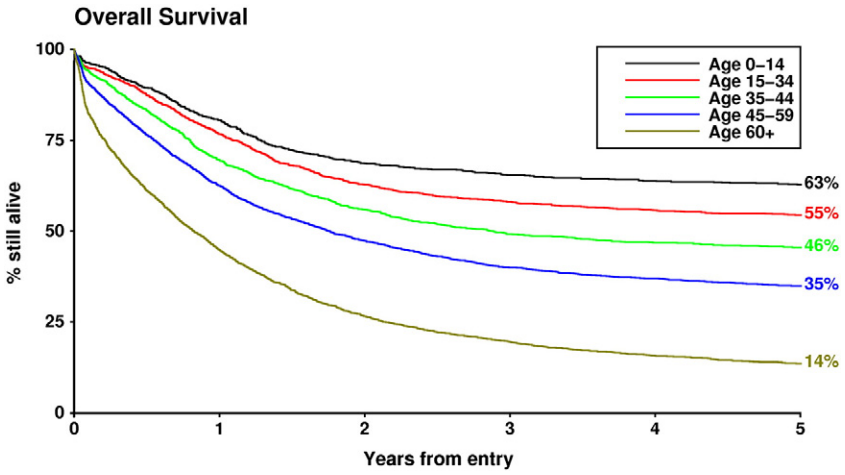

Fig. 1. Impact of age of presentation on outcome in AML. Survival of children and adults (n = 11,421) treated in successive Medical Research Council (MRC) AML trials (AML10, 11, 12, 14 and 15).

death rates and adverse survival in older patients receiving induction therapy[7] as well as outcome following allografting.[8]

2.2. Tumour burden

Clinical markers of a high tumour burden such as the presence of hepatosplenomegaly, a raised serum LDH[9] and a high peripheral blood white cell count (WBC) are associated with a worse prognosis even in the setting of otherwise good risk disease.[10–12] A high WBC is predictive of death in remission induction and a Canadian review of 375 patients found that a cut-off of 30×10^9/l was significant.[13] Outcome prediction could be refined if performance status was included, and this combined score was superior to consideration of age alone. Much of the prognostic impact of leucocytosis may reflect the molecular perturbation driving the proliferation, such as *FLT3* or *KIT* mutation. These will be discussed in detail in later sections.

2.3. Secondary AML

In approximately a fifth of AML patients the leukaemia is secondary, arising on a background of prior MDS/other haematological disorder (e.g. myeloproliferative disease) or is therapy-related following chemotherapy and/or radiotherapy for another condition. Secondary AML is becoming an increasing healthcare problem as the population ages and is associated with reduced CR and overall survival rates.[14]

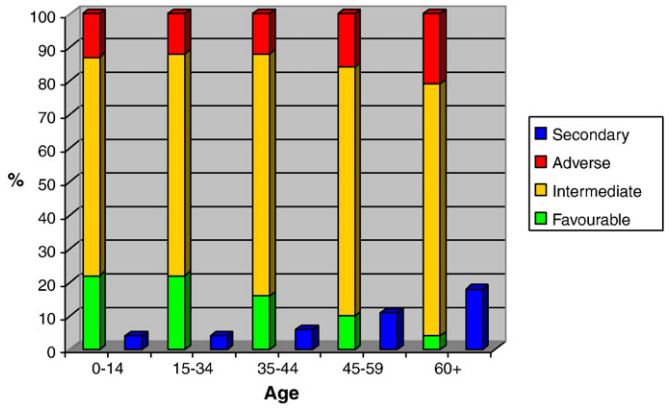

Fig. 2. Relationship between age of presentation and characteristics of AML (cytogenetic risk group and incidence of secondary disease). Based on analysis of 11,421 patients treated in successive Medical Research Council (MRC) AML trials (AML10, 11, 12, 14 and 15).

Traditionally therapy-related AML (t-AML) has been classified into two subgroups according to the nature of the agents to which the patient was exposed, which has an important bearing upon disease characteristics, biology, time to onset and prognosis. Treatment with drugs targeting DNA topoisomerase II predisposes to the development of leukaemias characterised by balanced translocations, particularly involving *MLL* at 11q23, *NUP98* at 11p15, *RUNX1* at 21q22 and *RARA* at 17q21. Such leukaemias typically present following a relatively short latency period (1.5–3 years) from time of first drug exposure, with no intervening myelodysplastic phase. In contrast, the other classic subtype of t-AML that arises after treatment with anti-metabolites, alkylating agents or radiotherapy tends to have a much longer latency period (typically 5–7 years), may be preceded by a myelodysplastic phase and is characterised by a complex karyotype often featuring loss or deletion of chromosome 5q and/or 7, and a high prevalence of *TP53* mutation.[15,16] However a major problem in distinguishing such subtypes of t-AML is that the majority of patients who develop this complication have been exposed to combination therapies that make it difficult to identify the causative agent in any particular case. This limitation is taken into account in the most recent World Health Organisation (WHO) classification of AML in which no distinction is made between cases arising following alkylating agents, radiotherapy or drugs targeting topoisomerase II, and which are categorised according to their cytogenetic and molecular features which more effectively capture disease biology and likely response to treatment.[17]

Therapy-related acute promyelocytic leukaemia (t-APL) with the t(15;17)(q22;q21) leading to fusion of the *PML* and *RARA* genes is particularly associated with previous breast cancer therapy involving epirubicin, mitoxantrone and/or radiotherapy and generally has a relatively favourable prognosis.[18,19] Patients with t-AML with chromosomal rearrangements involving genes encoding components of the core binding factor (CBF) haematopoietic transcription factor complex (i.e. with t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16)(p13;q22) leading to *RUNX1–RUNX1T1* and *CBFB-MYH11* fusions, respectively) may also have a relatively favourable prognosis (Fig. 3), although a recent relatively small single centre study has suggested that their outcome may be poorer than in patients with *de novo* CBF leukaemia.[20] Poorer outcome is generally observed in patients with secondary leukaemias involving the *MLL* locus at 11q23; while t-AML with loss of chromosome 5 and/or chromosome 7 material and cases with complex karyotype are associated with a dismal prognosis due to high rates of primary resistance and rapid relapse in those showing an initial response to chemotherapy (Fig. 3).

The new WHO classification also provides a list of structural and numerical cytogenetic abnormalities that are defined as “myelodysplasia-