The treatment of AML: Current status and novel approaches

ALAN K. BURNETT

Wales School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN

The epidemiology of AML suggests that in Western countries the median age of patients is around 65 years. Convention in recent years has often resulted in collaborative groups designing trials for patients under or over 60 years. In the former group treatment options included consolidation with stem cell transplantation of matched sibling allograft or autologous cells collected earlier in remission, which was not considered feasible in older patients.

Treatment in younger patients

It is now expected that complete remission (CR) can be obtained in 75–90% of patients under 60 years, usually with one course of treatment. Treatment mortality should be <10% with optimal supportive care. About 50% of patients who achieve complete remission will relapse, mostly over the next two years, so the overall 5 year survival at five years is around 50%. This represents an improvement of 1–1.5% per annum over the last 20 years. No single treatment modality accounts for this although intensification of treatment made possible by better supportive care seems the most plausible explanation [1,2].

Stem cell transplantation (both autograft and matched sibling allograft) has been carefully assessed in a number of major collaborative group trials [3–7]. This approach undoubtedly reduces the risk of relapse even in patients who have been treated intensively; however the impact on survival is less clear. The risk of relapse is dominated by a number of validated prognostic factors such as cytogenetics, FLT3 mutation status, the extent of blast clearance from the bone marrow after treatment course 1, presenting WBC and patient age [8,9]. Favourable risk cytogenetics includes (inv16); t(8;21) and t(15;17) and has an overall cure rate of 70–75%. Poor risk cytogenetics (abnormalities of Chs 5,7 3q-complex, t(9;22)) have a survival of 15%. All other lesions and normal have a survival of 50%. The presence of a FLT3 internal tandem repeat (ITD) mutation which itself significantly increases the relapse risk [10], adds refinement to the cytogenetic risk group – particularly the intermediate risk group (Relapse risk ITD+ve 70%; ITD-ve 45%). Mutations of RAS are present in 12% of patients, but do not appear to be prognostically important. As a general rule these prognostic factors are independent of treatment, including transplantation. Our recent analysis has been unable to show that there is benefit from transplant in FLT3 positive cases. Other mutations – although relatively rare, are being identified which may have prognostic value.

Numerous trials have been conducted over the years with the aim of determining which drug and dose combination is the most effective. Comparisons of anthracyclines, doses of Ara-C, the presence or not of a 3rd drug, have all been assessed without any convincing evidence of overall superiority for one schedule. Given the intensity of induction and consolidation, maintenance treatment is not indicated in younger patients. The precise total number of treatment courses required is not fully established but MRC studies suggest that the maximum should be 4 [11].

Once a patient relapses, his/her outcome is again dictated by prognostic factors more than treatment. These are age, length of first remission and cytogenetic risk group [12]. Patients who fail a transplant do less well, but this may in part be due to a reluctance to treat such patients intensively. Old age, short first remissions and adverse cytogenetics are virtually unsalvageable. Overall the outcome from relapse is about 20% without transplant, 35% with an autograft and 45–50% with an allograft (matched sibling or volunteer donor) [13].
Potential for improvement in younger patients
With a remission rate as high as it currently is, it will be difficult to show a benefit on remission rate of a new treatment with adequate statistical power. However it is well established but induction treatment – while not necessarily impacting on remission rate – can improve disease free survival by improving the “quality” of remission.

One of the interesting approaches currently in trial is adding in the immunoconjugate Gemtuzumab Ozogamicin (Mylotarg™). Initial studies at full dose (9 mgs/m²) suggested that unexpected liver toxicity would be problematic [14]. However a large study currently being conducted by the MRC confirms that adding Mylotarg in a reduced dose (3 mgs/m²) is feasible [15], however any benefit will not be known for 2–3 years.

Poor risk cases are particularly refractory, and although there is not unreal consistency in the evidence base such patients are usually offered allogeneic SCT (including MUD transplants) as soon as the risk status is known.

With the recognition of different molecular abnormalities, the expectation is that an era of molecularly targeted therapy – most likely in combination with existing treatments is imminent.

Treatment of older patients
The problem of treatment of older patients with AML has a number of facets [16,17]. First there is a substantial population of older patients who are not considered fit for the usual combination chemotherapy approach on offer due to age, frailty or comorbidity. Second, the success of effective treatment in younger patients is less successful in substantial part due to aggregation of adverse prognostic factors in older patients e.g., cytogenetics, prior MDS, and molecularly defined chemoresistance. Chemoresistance is defined by a number of proteins several of which may be coexpressed in the same patient. The most common and predictive is over expression of Pglycoprotein. Attempts to modulate the efflux action of the protein using the cyclosporine analogue PSC-833 have been unsuccessful [18,19]. Third, the survival has not – unlike in younger patients – improved much in the last two decades. Overall the current expectation of CR in an older patient is 50–60%. The relapse rate is high so overall the survival is 10–15% at 5 years.

Many randomized trials with large numbers have tried to improve outcome, with little clear success. This raises a further strategic issue in older patients, which is the question as to whether we should continue to focus clinical research and large numbers of elderly patients in large phase 3 trials as opposed to searching for novel against with a larger number of randomized phase 2 studies.

Transplantation in the older patient
Until recently it was accepted that standard allogeneic or autologous SCT in older patients carried a prohibitive mortality. However interest has been rekindled by the development of reduced intensity transplantation. This is clearly feasible with stable establishment of a full chimeric state. There does not yet seem to be a best choice preparative protocol. The slightly less reduced intensity will be strong enough to achieve full chimerism, but will often be accompanied by acute or chronic GVHD. More reduction in preparation intensity will reduce GVHD but may be associated with rejection.

Initially it was not thought that this transplant approach would be suitable for AML since several weeks are required to establish full chimerism. However a number of phase 2 experiences now suggest that durable survivals are seen in AML. However there is nothing to suggest that this approach has a survival advantage and it is important that this approach develops within the context of a prospective clinical trial. The improvements in tissue typing brought about by molecular matching of unrelated donors, has brought unrelated transplants to be a very practical option. Limited data suggests that this is also the case in older patients. These developments mean that allogeneic transplant is a viable option for older patients and is ready to be evaluated in clinical trials.

Novel agents
Given the lack of progress in older patients, and the probability that the molecular understanding of AML will bring new agents to the clinic, it is appropriate to direct new strategies and agents to the older patient.

Gemtuzumab ozogamicin [Mylotarg]
This immunoconjugate links a humanized anti-CD33 monoclonal antibody to the powerful intercalator calicheamicin. The key features are that the complex of CD33 antigen and antibody is rapidly internalized making it a potentially specific targeting vehicle for a chemotherapeutic agent. Since 90% of AML cases express CD33 and that expression is primarily on haemopoietic tissue this target is appropriate. A unique feature is that the clinical link joining the antibody to calicheamicin is only lysed intracellularly. Free calicheamicin is too toxic to give as a free agent so this is an important property.

Although only licences in the US and Japan for relapsed disease in the elderly. There is much interest in either combining it with chemotherapy – either simultaneously or sequentially – in or as maintenance
treatment in older patients. Pilot studies have confirmed the feasibility of this approach [15] but randomized studies will not be available for 3–5 years.

**Targeting FLT-3 mutations**

About 30–35% of younger patients and a lower proportion of older patients will have a FLT-3 mutation. As well as providing valuable prognostic information, FLT-3 mutation could provide a target for therapeutic targeting. At least 5 agents with in vitro activity against cells carrying a FLT-3 mutation have had some clinical evaluation (PKC412; CEP701; MLN518, SU5416) [20–24]. PCK 412 and CEP701 have been assessed in unrandomized phase 2 trials in patients with mutations. Although a degree of disease control was seen, no CR’s were obtained with it seems likely that in future these agents will be combined with chemotherapy. Second generation agents may be more effective but no clinical data is yet available.

**Farnesylation**

A number of cytoplasmic proteins, including RAS, which are involved in signal transduction, proliferation, angiogenesis and apoptotic pathways require to be prenylated. This process is mediated by the enzyme Farnesyl Transferase (FTase). FTase adds a 15-mer fatty acid chain to the C-terminal residue of substrate proteins which bear a –CAAX motif (farnesylation). This allows attachment to the inner surface of the membrane so facilitating binding of guanine nucleotide. While RAS may be an obvious target in AML, but disruption of other known or unknown proteins, may also be relevant. Tipifarnib (Zarnestra) is the agent which is most developed clinically in AML. Phase 1 in relapsed or refractory disease trials established a tolerable daily dose of 600 mg which can be given orally for 21 days a month. An unrandomized phase 2, involving trial patients, confirmed activity with a remission rate of around 25% in older patients not considered fit for intensive treatment. Activity was not restricted to patients with RAS mutations [25–27]. In spite of the convenience of an oral agent with activity as monotherapy, future interest will be in combination therapy. Clofarabine (2-chloro-2'-fluoro-deoxy-9-β-D arabinofuranosyl adenine is a rationally designed purine analogue. The design is intended to harness the potentially favourable profile of Fludarabine while avoiding the neurotoxicity associated with the dose of Fludarabine that is effective in AML, and resisting deamination. With the potential to become orally available Clofarabine. activity in advanced paediatric ALL lead to approval in the USA. Activity in AML has been established in a phase 2 trial in relapsed disease [28]. An unrandomized phase 2 study using a reduced dose as first line treatment patients who were not considered fit for intensive therapy [29]. A remission rate of 56% was observed with an acceptable toxicity profile although the degree of myelosuppression suggests that even a reduced dose was in fact intensive treatment. Nevertheless Clofarabine seems worthy of development either as a component of intensive treatment or at reduced dose for older patients.

**References**

The treatment of AML: Current status and novel approaches 53


