Management of Older Patients with Frailty and Acute Myeloid Leukaemia: A British Society for Haematology Good Practice Paper.

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Methodology

This Good Practice Paper was compiled according to the BSH process at [https://b-s-h.org.uk/]. The British Society for Haematology (BSH) produces Good Practice Papers to recommend good practice in areas where there is a limited evidence base but for which a degree of consensus or uniformity is likely to be beneficial to patient care.

Review of the manuscript

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Introduction

Acute myeloid leukaemia (AML) is a highly heterogeneous haematopoietic stem cell malignant disorder and the most common malignant myeloid disorder in adults, with a median age of 70 years at presentation[1]. Within this good practice paper we update on developments specific to the older AML patient with frailty (a distinctive health state related to the ageing process in which multiple body systems gradually lose their in-built reserves) where, historically, the potentially more effective intensive therapies have not been considered standard-of-care. Age is a significant adverse prognosticator, associated with a decreased complete remission (CR) rate, disease free survival (DFS), and overall survival (OS), with higher rates of treatment related mortality (TRM), resistant disease and relapse compared to equivalently treated younger patients[2,3]. OS rates with recent standard non intensive therapies are poor [,5]. AML in older patients commonly evolves from myelodysplastic syndromes (MDS)

or myeloproliferative neoplasms (Heinemann and Jehn 1991) and is associated with adverse karyotypes[1,6] and frequent unfavourable mutations. In combination, these result in inferior responses to therapy, refractory disease and more frequent infectious complications[7,8].

In recent years, the role of mutations in both driving the malignant process and determining the response to novel treatment approaches such as small molecule targeted treatments, bispecific antibodies and liposomal chemotherapeutic agents has become clearer[9]. Whilst improvements in supportive care and regimen intensification have been beneficial in younger AML patients, the effects have not been seen in the elderly. Even the few older AML patients who can tolerate, and therefore benefit from, intensive remission-induction approaches[10] suffer increased toxicity[11] with increased early mortality (almost 30% at 8 weeks). Most are best managed with less aggressive strategies[12]. Unlike younger AML patients, psychosocial factors such as cognitive decline and the presence of adequate social support[13] factor into treatment decisions.

The challenge in treating older adults with AML is to adequately address both patient factors and disease related biological features, in order to maximise the therapeutic benefit and minimise toxicity.In this good practice paper, we review the clinical management of older patients, generally not considered suitable for intensive chemotherapy or stem cell transplantation, a similar guideline approach has recently been published by the American Society for Hematology[14]

Diagnostics

The revised 2016 WHO classification[15,16] updated the classification of AML, and AML diagnosis remains organised according to a number of cytogenetic abnormalities or gene mutations. Older adults who are suspected of having AML and are deemed to

be fit to receive anti-leukaemia therapy, should undergo the same diagnostic workup as any other patient (Table 1). Diagnostic specimens should be sent to the appropriate specialist diagnostic laboratory, in line with National Institute for Health and Care Excellence (NICE) guidance[17], and the final integrated report should be discussed in a multi-disciplinary team setting, including clinical and laboratory staff. The growing availability of targeted treatments means that it is imperative that older patients with AML, who are more likely to have unfavourable risk cytogenetics[1], have their disease comprehensively assessed in a timely fashion to ensure that they can be offered the most appropriate therapy.

At Diagnosis

Patients should have a bone marrow examination (aspirate and trephine biopsy) for blast enumeration (with a 300 cell or 500 where indicated differential cell count[18]) and flow cytometry to characterise the leukaemic clone immunophenotype to confirm lineage, and because this provides a means of assessing measurable residual disease (MRD) in the absence of a molecular marker[19]. For patients with a high white blood count at presentation, diagnostic workup may be performed on the peripheral blood *in lieu* of a bone marrow examination, and this may also be a suitable approach for the frail patient for whom best supportive care is the most appropriate treatment option. Consideration should also be given (with appropriate patient consent) to taking trial samples at the time of diagnostic marrow sampling.

Risk stratification remains informed by cytogenetic analysis and given that some treatments (e.g., CPX-351) are currently only licensed in the UK for therapy-related AML or AML with myelodysplasia-related changes (AML-MRC), knowledge of cytogenetic abnormalities is a prerequisite to offer the most appropriate treatment. Genomic classification has increasing therapeutic relevance and the National

Genomic Test Directory for Cancer (https://www.england.nhs.uk/publication/national-genomic-test-directories/) currently recommends screening for mutations in several genes (see Table 1). This is likely to be most efficiently achieved using a multi-target next-generation sequencing (NGS) panel approach with a maximum turnaround time of 21 days. However, we recommended rapid screening (turnaround time within 72 hours) for mutations of *NPM1*, *FLT3*, *IDH1*/2 and *TP53*, given that the presence of *NPM1* and *IDH1*/2 mutations may inform treatment decisions (these mutations have been shown to confer a superior response to venetoclax/azacitidine[20]), whilst *TP53* mutations confer resistance to chemotherapy and an overall poor outcome[21].

At Relapse

At relapse, patients who remain fit to receive anti-leukaemia therapy, should be re-screened for actionable/targetable mutations. At the least, this should include re-screening for mutations in *FLT3* (both internal tandem duplication; ITD and tyrosine kinase domain; TKD), given the availability of gilteritinib[22] in this setting, as well as *IDH1*/2 mutations (if trial recruitment is an option). It should be noted that *FLT3* mutations may be acquired or lost at relapse[23], and it is therefore important to reassess for their presence.

Recommendations:

- **All patients should have their disease assessed by morphology, immunophenotyping, cytogenetics and molecular studies at presentation.**
- **At relapse, patients should be re-screened for *FLT3* mutations as a minimum.**
    - **Peripheral blood is a suitable alternative to bone marrow for the diagnostic evaluations if there are circulating blast cells.**

- **All cases should be discussed at an appropriate local or regional haemato-oncology MDT**

Evaluation of Ability to Tolerate Therapy (Comorbidity Assessment and Mortality Prediction)

Evaluation of fitness for treatment in older AML patients

All patients should be assessed for their suitability to receive intensive induction therapy at presentation. Personalised plans, for treatment and survivorship, that account for heterogeneity of ageing and address patient-centred goals such as quality of life, are needed. Although chronological age is informative, it should not be the sole determinant of suitability of a patient for intensive therapy. Different algorithms using chronological age, performance status and cytogenetic/molecular data have been used to determine the probability of CR, early mortality and survival[24,25] but have not been adopted widely into clinical practice as decision making tools.

Comorbidities

The likelihood of comorbidities increases with age and can affect treatment administration and toxicity[1,26,27]. Patients with comorbidities are often excluded from clinical studies, limiting data to inform treatment decisions. However, comorbidity indices, such as the Charlson comorbidity index (CCI) and the Hematopoietic Cell Transplantation–specific Comorbidity Index (HCT-CI), have been validated for prediction of outcome in AML patients[28,29]. The HCT-CI includes objective definitions of comorbidities as well as an assessment of their level of severity[30,31]. Among 177 AML patients aged >60 years and treated with intensive chemotherapy, those with an HCT-CI score ≥3 had an early mortality rate of 29% versus 3% and 11% in

patients with scores of 0 and 1–2, respectively (P<0.001)[29]. However, ageing and frailty related to ageing are not entirely a function of comorbidities. Patients with several well-managed comorbidities may be reasonably fit and vice versa. Thus, patients should have an assessment of comorbidities and frailty to better define fitness for intensive therapy[30].

Performance Score (PS)

Oncology PS measures, such as the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) or the Karnofsky PS (KPS), can aid in identifying higher-risk AML patients independently of age. Treatment toxicity assessed by early mortality is higher in older adults with poor PS[32]. A retrospective analysis assessed outcomes and prognostic factors for 998 patients aged ≥65 years with AML or high-risk MDS receiving intensive therapy between 1980 and 2004[33]. A multivariate analysis in these patients identified poor ECOG PS (>2) among the prognostic factors associated with worse CR rate, 8-week mortality, and OS[33]. An analysis of 2767 AML patients in the Swedish Acute Leukemia Registry evaluated the effect of the decision to treat on outcomes[34]. In this study, 30-day mortality rates were dependent on both age and PS; however older patients with good PS had low early death rates and patients with poor PS had increased early mortality across all ages. Early death was reported for 36% of patients aged 76–89 years with a PS of 3–4 who were given intensive therapy versus 52% of patients who received palliation only (P=0.023). While the early mortality rate was higher in patients with impaired PS across age groups, there were some long-term survivors, suggesting intensive therapy may be of benefit for selected patients[34].

Comprehensive Geriatric Assessments

Geriatric assessment (GA) provides a multidimensional characterisation of an older adult, including physical and cognitive function, socioenvironmental status, nutrition, psychological health and medications. The use of comprehensive geriatric assessments (CGA) can help unmask vulnerabilities in older patients and can be used to categorise patients as 'fit', 'prefrail/ vulnerable' or 'frail'. Multiple GA tools have been evaluated in the haematology setting including in AML (Table 2), and have been shown to be predictive of treatment-related toxicity and survival outcomes[35,36].

The geriatric domain with best evidence supporting prognostic value is physical function and this can be assessed by patient reported surveys such as activities of daily living (ADL) and can be objectively measured using specific tests such as short physical performance battery (SPPB- gait speed, balance, get up to go, grip strength)[35]. Cognition and polypharmacy have also been shown to predict survival independently in intensively treated AML patients[32] and should be assessed and managed with the help of specialists. Indeed in a recent randomised clinical trial of patients with AML, integrated oncology and palliative care led to substantial improvements in quality of life, psychological distress and end of life care[37].

Recommendations:

- **All patients should be evaluated for their ability to tolerate intensive chemotherapy – this should be on the basis of geriatric assessment (GA) with emphasis on premorbid performance status, physical function and comorbidities. In general, a score of >10 on Edmonton frailty scale, >3 on HCT-CI and >2 on ECOG PS would be at a higher risk for treatment related**

morbidity and mortality with intensive chemotherapy (See appendices 1-3 for recommended GA including age, comorbidities, performance score).

- **Where possible, assess organ function/comorbidities with specialists and tests e.g. echocardiography (ECHO), lung function tests, to aid treatment decisions. Develop the use of a geriatric assessment tool in your local setting.**
- **Those considered 'fit' should be additionally evaluated for the most appropriate treatment according to the biological diagnostic features of the AML.**

Supportive Care

Transfusion

It is standard practice in the UK that cellular blood products are leucodepleted. In recent years, all blood products used routinely are cytomegalovirus (CMV) unselected. Comprehensive transfusion guidelines are available at https://b-s-h.org.uk/guidelines/.

Antimicrobials

Antibiotic prophylaxis with quinolones such as ciprofloxacin can be considered in patients at risk of febrile neutropenia or with severe protracted neutropenia when receiving chemotherapy and should be guided by local antimicrobial policy. The importance of local microbiology resistance patterns should be taken into consideration when deciding on quinolone prophylaxis in high-risk neutropenic patients. A Cochrane review demonstrated that the use of prophylactic antibiotics when compared to placebo is effective in reducing overall mortality and infection-related mortality in neutropenic patients[38]. This effect is most marked in individuals

receiving quinolone antibiotics[39] such that European Leukamia Net recommends their use[2] . Posaconazole or another mould-active azole is essential to prevent invasive fungal infections during remission-induction therapy and in patients with prolonged neutropenia[2, 40,] . Herpetic virus reactivation is common in the older frail population, a systematic review by the Multinational Association of Supportive Care in Cancer /International Society of Oral Oncology showed that aciclovir is effective in preventing oral herpetic viral disease in patients with hematologic malignancies[41] prophylactic aciclovir is relatively common in clinical practice and recent guidelines support this approach[42] .

Baseline human immunodeficiency virus (HIV) and hepatitis B/C serology must be checked prior to starting chemotherapy and patients with past or active hepatitis B/C should receive appropriate prophylaxis and be discussed with a hepatologist/virologist.

Yearly influenza vaccination with inactivated vaccine is recommended for all patients receiving chemotherapy, for all family and household contacts, and for health care providers. Guidance related to COVID-19 is discussed below.

Symptom Management

Supportive treatment with antiemetics, antidiarrhoeals and analgesia are vital aspects of patient care. Early involvement by the palliative care team for symptom management is recommended. Older patients undergoing chemotherapy can be particularly vulnerable to anxiety, depressive symptoms, weight loss, fatigue and lack of social support. Polypharmacy is common so vigilance for drug interactions is required. A multidisciplinary team including dieticians, nurse specialists, physiotherapists and occupational therapists along with clinical psychology support will help patients through their disease course.

Recommendations:

- **Supportive care with transfusion therapy and antimicrobials is less evidence based in the older AML patient but has become established practice.**
- **Patients on disease modifying therapy, which induces significant neutropenia, should have primary prophylaxis with a quinolone antibiotic, mould-active azole and aciclovir, in accordance with local prescribing practice.**
- **Preservation of quality of life is a key goal and timely involvement of palliative care and community teams should be encouraged.**

Less Intensive Chemotherapy

Low dose Cytarabine

Low dose Cytarabine (LDAC) became the standard non-intensive approach for older patients following the results of the AML14 study which showed a marked median survival advantage for LDAC compared to the previous standard-of-care[43]. In this study, 18% of patients receiving LDAC 20 mg bd for 10 days in a repeating 28-day cycle achieved a CR compared with 1% on standard-of-care. Those who achieved CR, after a median of 114 days treatment, had a significantly longer survival compared with non-remitters: 19.1 months v 2.2 months. Despite this improvement, OS remained poor with 2-year survival of around 9%. All of the advantage of LDAC was seen in patients with favourable or standard risk cytogenetics, with no CRs in unfavourable risk patients. Subsequently, more extensive experience in the Li1 trial has confirmed that few patients with adverse cytogenetics or *FLT3*-ITD respond to LDAC[44,45]. Significant side effects include marked cytopenia and blood counts may

worsen initially. The median time to response is 95 days (3 cycles of treatment); with fewer than 25% of responders achieving complete remission/complete remission with incomplete hematologic recovery (CR/CRi) within 60 days[44]. Hence, for patients tolerating treatment, it is important to persevere with these treatments even if not achieving CR with the initial cycles.

Azacitidine

Azacitidine is a hypomethylating agent (HMA) recommended by NICE for use in patients with high-risk MDS or AML with fewer than 30% bone marrow blasts[46] based on the MDS001 study[47,48]. Although there is evidence of efficacy in AML with higher blast percentages with similar CR rates compared to conventional chemotherapy (27.8% v 25.1%)[49] our recommendations follow the NICE guidance. Patients who respond have a significantly improved OS (12.1 months v 6.9; p=0.019), with a trend to improved survival even in the absence of true CR[41]. Initial studies gave azacitidine 75 mg/m^2 on seven consecutive days. It is now conventionally given for 5 days, with a 2-day break over a weekend, followed by 2 days in the second week – the so-called 5-2-2 schedule. There is no evidence that this divided dosing impairs efficacy. Most patients will experience marked thrombocytopenia with therapy, although this usually recovers and early recovery of platelet counts may predict response[50]. If prolonged cytopenia occurs, the dose of azacitidine will need to be reduced, either by reducing the daily dose, or the number of days of therapy, or by increasing the interval between cycles. The interval should not be increased beyond 6 weeks as it is less likely to be effective at longer intervals. Treatment should be continued for as long as there is haematological benefit. Historically recommendations have been to give a minimum of 4 cycles of therapy, however depending on availability of emerging therapies this may no longer be valid.

Decitabine is another HMA approved by the European Medicines Agency (EMA) for patients with newly diagnosed de novo or secondary AML who are not candidates for standard induction chemotherapy. NICE technology evaluation has not been sought, and as a consequence, its use within the UK is largely confined to clinical trials. Within a large real-world data retrospective study in the US[51] there were no differences in survival between decitabine and azacitidine.

Venetoclax

Venetoclax is an oral synthetic inhibitor of the anti-apoptotic protein BCL2 that is overexpressed in AML cells. BCL-2 mediates resistance to apoptosis by sequestering the pro-apoptotic protein BAX. The inhibition of BCL2 by venetoclax releases BAX, resulting in permeabilisation of the mitochondrial outer membrane and apoptotic cell death in AML and other malignancies[52,53].

Venetoclax was approved by the Food and Drug Administration FDA in 2018 for the treatment of newly diagnosed elderly AML patients, ineligible for intensive chemotherapy, in combination with either HMA or LDAC. The EMA approved venetoclax in combination with azacitidine in May 2021, interim approval by NHS England for treating subtypes of AML in patients aged over 50 years deemed fit for intensive chemotherapy was possible during the COVID-19 pandemic[54] and finally NICE approval was confirmed December 2021.

The early phase studies[55,56] of venetoclax combined with HMA or cytarabine, demonstrated efficacy with composite CR rates in excess of 60%, with similar response for secondary AML, median time to response of 1.2 months and low treatment-related mortality of 3-6% at 30 days. The follow-on VIALE- A phase 3 study randomising venetoclax combined with azacitidine vs azacitidine alone established improved OS (14.7 vs 9.6 months, hazard ratio for death, 0.66; 95%

confidence interval, 0.52 to 0.85; P<0.001) for the combination in untreated patients with AML over the age of 75 years. The VIALE-C study randomising to venetoclax or placebo combined with LDAC did not reach its primary endpoint of establishing a significantly better OS, although a post hoc analysis showed improved survival in the combination arm[57].

High response rates and durable remissions occur in those patients with *IDH1*/2 and *NPM1* mutations (median response duration 21 and 49 months, respectively). Most of the *NPM1*-mutated AML patients achieved MRD negativity[58]. For the subgroup with *NPM1*-mutant AML, the cytarabine combination has similar efficacy to the azacitidine venetoclax combination and is a suitable alternative. The combination showed efficacy in patients who had prior treatment with HMA although at a reduced rate. *TP53* or *FLT3* mutations had lower CR/CRi rates (30% and 44%, respectively)[59]. As these response rates are superior to existing therapies, the combination is recommended for treating all subtypes of AML. Whilst there is clinical interest in a switch of venetoclax partner from azacitidine to cytarabine where there is disease resistance or intolerance currently data of efficacy is lacking.

Recommended dosing schedules are outlined in Table 3. Consideration should be given to admitting the patient to initiate administration of the first cycle of treatment where there is a potential risk of tumour lysis syndrome (TLS) (eg high circulating blasts, favourable molecular profile or pre-existing renal impairment),however the incidence of TLS is low and therapy is increasingly administered in an ambulatory setting for stable patients. In general, venetoclax is well tolerated with nausea, diarrhoea, constipation, decreased appetite, hypokalaemia and fatigue as the main side effects. Cytopenias are frequent and dose adjustment, by reducing the duration of venetoclax, is necessary between cycles for prolonged neutropenia. Response to

the combination is rapid[60]. In VIALE A the median time to response of 1.0 month and median time to best response of 2.1 months. 65% of the responses to meet CR/CRi criteria occurred by C1; 76% by two cycles, a further 9% achieved this by cycle 4 and 9% by cycle 6. The comparative responses for VIALE C was CRc achieved in 41% by C2 and 8% responded beyond C2. In both studies achievement of a morphological leukaema free state by Cycle 2 predicted for later responses, A 50% reduction in bone marrow blast percentage compared to baseline also predicted for late responses. In addition, for those achieving CRc, the achievement of a >3 log reduction (flow MRD) first occurred by the end of C1 in 25%; C4 in 27%, C7 in 27% with 21% taking longer. The median duration of response was not reached in patient who achieved this level of MRD at any time[61]. (Pratz K, Jonas B,Pullarkat V et al Minimal Residual disease response and prognosis in Treatment Naïve Acute Myeloid Leukamia with Venetoclax and azacytidine . JCO 2022: 40; 855-865). Although the optimal number of cycles has yet to be determined, MRD monitoring should be utilised where applicable eg. *NPM1* molecular monitoring.Treatment should be continued until the patient loses response or experiences severe toxicity. In practice, monthly cycles are given for the first 4 cycles and 6–8 weekly thereafter, dependent on the recovery of blood counts and patient tolerance. The use of granulocyte colony-stimulating factor (G-CSF) is recommended to aid neutrophil recovery once a bone marrow examination demonstrates blast clearance. Patients with an MRD marker should have stringent MRD monitoring to assess response to venetoclax combinations and guide therapy.

The bulk of primary or adaptive resistance to venetoclax is accounted for by activating mutations in kinase signalling pathways such as *FLT3*, *RAS* or biallelic mutations/disruptions of *TP53*[9]. Treatment of refractory cases need to take into

account the relevant mutational resistance pattern with *FLT3*-TKD displaying resistance to quizartinib and sorafenib[62]; *FLT3* N676 displays resistance to midostaurin[63] and *NRAS* mutations resistance to giltertinib[64].

The perceived frailty or deterioration in performance status of patients usually improves following the achievement of remission, this allows ongoing maintenance type therapy in the ambulatory setting. The are however a number of retrospective studies which have identified the possibility of allogeneic transplant for a small minority of such patients which encouraging outcomes[65,66].

Recommendations:

- **The new standard therapy for older AML patients considered unfit for intensive chemotherapy is venetoclax and azacitidine.**
- **Venetoclax combined with LDAC is an alternative combination for those patients with *NPM1* mutation.**

Secondary Disease

Secondary AML may represent 25-30% of all cases[67]. It is associated with an adverse outcome compared to de novo disease due to increased disease resistance, relapse and accumulation of secondary genetic lesions[68]. Non-intensive options, including monotherapy LDAC and azacitidine, are used but have limited effectiveness and, like primary disease, are now managed with venetoclax combinations. CPX-351 has recently been approved as an intensive therapy option for patients with secondary AML[69]. This liposomal formulation of fixed ratio cytarabine and daunorubicin avoids some toxicity of conventional chemotherapy but is still associated with cytopenia and septic complications, attenuated schedules designed for the older AML patient with frailty remain investigational.

Emerging Targeted Therapies

The last 3 years has seen the approval of several targeted therapies for the treatment of AML. This has enabled patients with specific molecular lesions, e.g., *FLT3*-ITD/TKD or *IDH1* or *IDH2* mutation, to benefit from orally delivered targeted approaches. However, there are restrictions on when, and to whom, these drugs can be prescribed, so not everyone will have the opportunity to benefit. Table 4 provides an overview of approvals with specific relevance to the elderly population.

Midostaurin inhibits multiple receptor tyrosine kinases, including FLT3 and KIT. Following a positive outcome in the RATIFY trial[70], it is NICE/Scottish Medicines Consortium (SMC) approved for patients with newly diagnosed *FLT3*-mutated AML, providing it is administered with standard daunorubicin and cytarabine induction therapy. In 2020, the third generation FLT3 inhibitor, gilteritinib was NICE/SMC approved as monotherapy for adult patients with relapsed or refractory *FLT3*-mutated AML, following data from the ADMIRAL trial showing the superiority of gilteritinib to conventional chemotherapy in this setting, only a small proportion of the study population received low intensity chemotherapy with a median duration of only 4 weeks highlighting the lack of efficacy with treatment such as LDAC and AZA[22].

Ivosidenib and enasidenib are orally available, targeted inhibitors of mutated IDH1 and IDH2, respectively. Both are FDA approved for IDH1/2-mutated relapsed or refractory AML based on the positive results from early phase, single arm clinical trials[71,72]; neither agent is approved in Europe or the UK, although further clinical trials are ongoing, including combination regimens, in both the newly diagnosed and relapsed/refractory setting.

For those patients who do not have a specific targetable mutation, therapies that target proteins or pathways common to many different AML subtypes are

425 increasingly being explored. For example, the CD33 monoclonal antibody-drug
426 conjugate gemtuzumab ozogamicin (GO) is approved for use in patients with newly
427 diagnosed AML, in combination with daunorubicin and cytarabine, who have either
428 favourable, intermediate or unknown cytogenetic risk, but not known adverse risk.
429 This is based on data from several clinical trials showing improved outcomes for
430 patients receiving GO[73,74]. Monoclonal antibodies targeting the cell surface
431 molecules CD47 (magrolimab)[75] and CD70 (cusatuzumab)[76] are in early phase
432 clinical trials in AML, including in elderly patients with relapsed/refractory disease
433 and appear to be well tolerated with some efficacy, but additional data is urgently
434 needed. Other approaches that show some promise in AML are targeting self-
435 renewal pathways, cell cycle or apoptosis, usually in combination with conventional
436 therapy. For example, the smoothened (SMO) antagonist, glasdegib, has been
437 approved by the FDA, in combination with LDAC for the treatment of elderly patients
438 with newly diagnosed AML[77]; it is not yet approved in Europe or the UK. Several
439 MCL1 inhibitors are being combined with venetoclax in early phase clinical trials and
440 results are eagerly anticipated[78].

441 **Management of Relapse**

442 The median survival for elderly patients with relapsed AML is measured in months,
443 hence the management of relapse in this scenario is generally considered palliative.
444 For patients wishing to explore experimental therapies, early consideration of an
445 investigational approach in a trial or extended access programme should be
446 undertaken. Particular issues likely to influence management decisions in this
447 population include frailty, co-morbidities, distance from treating centre and availability
448 of caregiver or social support.

At the time of relapse, evaluation should focus on patient fitness and holistic decision making as to whether further therapy is appropriate.

In conclusion, management of relapse in the elderly or unfit is complex, requiring understanding of the interplay of disease characteristics, psychosocial scenarios, fitness, and analysis of the benefits versus otherwise of potentially toxic therapies. Given the very poor prognosis in this situation, where possible we strongly recommend exploration of the possibility of clinical trials for this patient population.

Recommendations:

- **All patients should have their disease assessed by morphology at relapse; immunophenotyping, cytogenetics and molecular studies are also indicated for select patients at relapse.**
- **A previous good response to therapy may encourage a repeat challenge.**
- **Investigational approaches may be appropriate for patients who have targetable lesions, lack comorbidity and have a good performance status.**
- **Survival from relapse is short with palliative care usually being appropriate.**

Clinical Trials

This patient population has historically contributed low recruitment to clinical trials due to ineffective therapies, adverse disease biology and physical limitations of the older AML patient – thus the population has not been well served by conventional clinical trials. However, with relatively short survival, innovation can rapidly lead to patient benefit as seen with venetoclax.

Some trial designs, most notably “Pick-a-winner”[70], have allowed enrolment of a small number of patients to consider the efficacy of the agent with regard to a

survival surrogate (remission). Progression of the agent towards comparison of survival against standard-of-care, may include the initial patients and can happen contemporaneously with review of other agents. Where remission is accepted as a suitable surrogate, this design improves efficiency of evaluating multiple new therapies sequentially[79].

Whilst emerging therapies will be required to demonstrate an improvement in OS, regulatory drug approval agencies accept improvement in Quality of Life (QoL) as a criterion for drug approval and QoL has received some attention in this patient population. Data[80] suggest that patients who achieve CR demonstrate improved QoL. However, further work is required to consider more focused tools for QoL and Patient Reported Outcomes Measures (PROMs) and to include patients not currently served by treatment trials.

Inclusion of several collaborative groups has accelerated completion of some trial protocols in this population. In order to recruit to sufficiently powered questions in genetic profile designated sub-populations, in this rare disease, wider international collaboration is essential.

Recommendations:

- **Older patients with AML continue to have a short life expectancy – clinical trials present an opportunity for improving outcome and should be considered in all patients at presentation and relapse.**
- **Future research is needed to extend findings with a focus on reserve capacity, resilience, quality of life and the effectiveness of non-oncological interventions.**
- **Novel trial designs that serve this rare complex population are warranted.**

Special Situations

COVID-19 and AML

Patients may present with **co**rona**vi**rus **d**isease 20**19 (**COVID-19) at the time of diagnosis of AML or, more probably, during their treatment for AML. Such patients should be managed in isolation facilities, or in cohorts and this presents challenges for the delivery of chemotherapy. NICE has issued rapid guidance for blood and marrow transplantation during the pandemic (NG164) and the National Cancer Research Institute (NCRI) AML Subgroup has issued guidance for chemotherapy in AML[54]. Consideration should be given to minimising the amount of time spent in hospital, delaying/deferring treatment where possible.

Acute Promyelocytic Leukaemia

Acute promyelocytic leukaemia (APL) is relatively rare in the older AML patient; early mortality rate in clinical trials was high and ranged between 10 and 18%[81,82]. Early deaths occur due to bleeding and from infections/sepsis or multiorgan failure.[1,2,3] Registry data further demonstrate that age over 60 years was associated with a significantly shorter OS, mainly influenced by the high rate of early mortality[83–86].

Once APL is suspected, all-*trans*-retinoic acid (ATRA) should be initiated immediately. Due to the high incidence of early mortality, transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh-frozen plasma should be given to maintain the fibrinogen concentration above 1.0-1.5 g/l, platelet count above 30-50 x 10^9/l and the International Normalised Ratio (INR) below 1.5[87].

Older patients are able to achieve durable remissions and hence should be treated with this intention.

High risk fit older patients with high-risk APL (white cell count >10 x 10^9/l) can be treated with a similar treatment approach to that used in younger patients, although dose reduction should be considered with chemotherapy (especially anthracyclines)-based regimens[87-90]. Patients with a high white cell count >10 x 10^9/l should receive prophylactic corticosteroids which can potentially reduce the risk of APL differentiation syndrome[87,89]. Dexamethasone 10 mg intravenously twice a day should be started immediately at the earliest clinical suspicion of APL differentiation syndrome.

Standard risk: standard risk patients are candidates to receive arsenic trioxide (ATO)-based regimens. Results from two randomised trials have shown safety and efficacy of an ATO plus ATRA approach in older patients[90,91].

Recommendations:

- **Remission rates and early mortality are high – as with APL in younger patients immediate supportive measures and ATRA treatment are mandated. ATRA and ATO are suitable for most patients.**
- **High risk patients should be considered for dose-reduced idarubicin based therapy.**

Extramedullary Manifestations

Extramedullary manifestations of AML include myeloid sarcoma (granulocytic sarcoma or chloroma) and leukaemia cutis. Baseline imaging with computer tomography (CT), positron emission tomography-CT (PET-CT) or magnetic resonance imaging (MRI) can help with diagnosis and monitoring treatment response and should be part of the initial diagnostic work-up where extramedullary disease is suspected.

Treatment options include chemotherapy (intensive or non-intensive) or localised radiotherapy. Older patients unfit for chemotherapy may be offered localised palliative radiotherapy for symptom control.

Summary

Older patients with AML account for nearly half of those with the disease. Because they are perceived to be unfit, unwilling, or unlikely to benefit from conventional intensive chemotherapy they represent an important unmet need. The observation that LDAC improved survival and apparent QoL compared to best supportive care established a standard-of-care for the older AML patient. The introduction of HMAs improved survival without substantially improving the rate of remission and became globally considered the new standard. Newer combinations show considerable promise, and indeed have received regulatory approval for this patient group. Venetoclax combinations are the new standard-of-care – the challenge is now to investigate their optimal use in treatment algorithms based on patient and disease profile. Future evaluations with additional or alternative partner therapies based on disease biology should improve the prognosis for such patients further.

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Declaration of Interests

All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. The following authors have undertaken and then please detail any advisory board, educational grant, and speaker's fees for the different companies or charities etc. declared by the writing group members – monetary details are not required. The following members of the writing group list initials have no conflicts of interest to declare.

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Tables/Figures

Table 1: Diagnostic Investigations for AML in the Older Adult

Diagnostic	Diagnosis	Relapse
Bone marrow aspirate	√	√
Bone marrow trephine biopsy	√	√
Flow cytometric immunophenotyping	√	√
Cytogenetic analysis (G-banding and FISH panels) (within 5 working days)	√	√[a]
Rapid *FLT3* ITD and TKD mutation screen (within 72 hours)	√	√
Rapid *NPM1* mutation screen (within 72 hours)	√	
Multi-target NGS panel including minimum of: *IDH*1/2 screen *TP53* screen *ASXL1* screen *RUNX1* screen	√ √[b,c] √[b,c] √ √	

Abbreviations:AML, acute myeloid leukaemia; FISH, fluorescence *in situ* hybridisation
a If no unfavourable risk cytogenetic abnormalities were found at diagnosis, or if the patient has experienced a prolonged remission (>12 months), then cytogenetics should be rechecked at relapse. b Rapid mutation screening assays for *IDH1/2* and *TP53* are recommended as these mutations may impact early treatment decisions.
c National Genomic Test directory for Cancer (https://www.england.nhs.uk/publication/national-genomic-test-directories/) currently recommends screening for mutations in following genes at diagnosis; *NPM1*, *CEBPA*, *RUNX1*, *FLT3*, *IDH1*, *IDH2*, *KIT*, *WT1*, *ASXL1*, *SRSF2*, *STAG2*, *RAD21*, *TP53*, *KRAS*, *NRAS*, *MLL* (*KMT2A*)-PTD, *PPM1D*

Table 2 Geriatric Assessment Domains

Geriatric Assessment Domain	Tests/tools Used
Comorbidity	Charlson Comorbidity Index (CCI) Cumulative Illness Rating Scale-Geriatric (CIRS-G) Hematopoietic Cell Transplant-specific Comorbidity Index (HCT-CI)
Cognition	Blessed Orientation-Memory-Concentration (BOMC) Mini-Mental State Examination (MMSE) Modified mini-mental state examination (3MS)
Mental Health	Hospital Anxiety and Depression Scale (HADS) Geriatric Depression Scale-15 (GDS-15) Mental Health Inventory-17 (MHI-17) Medical outcomes short form-36 health-related quality of life questionnaire-Mental Component Score (SF36-MCS)
Functional status	Activities of Daily Living (ADL) Instrumental Activities of Daily Living (IADL) Eastern Cooperative Oncology Group Performance Status (ECOG PS) Karnofsky Performance Status (KPS) Medical outcomes short form-36 health-related quality of life questionnaire (SF36-PCS) Falls Short Physical Performance Battery (SPPB) Grip strength Timed up and go test Walk speed
Frailty	Fried frailty index Rockwood Frailty scale The Edmonton Frailty scale
Nutrition	Body Mass Index (BMI) Weight loss Serum albumin
Polypharmacy	Number of medications
Social support	Medical Outcomes Study (MOS) social activity limitations/social support subscales
Quality of life	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

Table 3: Dosing Recommendations for Venetoclax from the NCRI AML Working Party

The following treatment schedule is recommended (other schedules may be used according to established local practice)	
Azacitidine schedule	• Azacitidine 75 mg/m² SC, once a day D1-7 (or D1-5 and D8-9) • Venetoclax (cycle 1) 100 mg D1, 200 mg D2, 300 mg D3 and 100 mg* D4-D28 orally once daily • Cycle 2 onwards: Venetoclax 100 mg D1-D28 orally (see below for guidance on changing number of days per cycle) • Posaconazole (cycle 1) 300 mg twice daily on D4 and once daily on D5-28 (cycle 2 onwards) 300 mg once daily on D1-D28 or • Voriconazole (cycle 1) 400 mg twice daily on D4 and once daily on D5-28 (cycle 2 onwards) 200 mg twice daily on D1-D28
Cytarabine schedule	• Cytarabine 20 mg/m2 SC once a day on D1 to 10 • Venetoclax (cycle 1) 100 mg D1, 200 mg D2, 300 mg D3 and 100 mg* D4-D28 orally once daily • Cycle 2 onwards: Venetoclax 100 mg D1-D28 orally (see below for guidance on changing number of days per cycle) • Posaconazole (cycle 1) 300 mg twice daily on D4 and once daily on D5-28 (cycle 2 onwards) 300 mg once daily on D1-D28 or • Voriconazole (cycle 1) 400 mg twice daily on D4 and once daily on D5-28 (cycle 2 onwards) 200 mg twice daily on D1-D28
Dose adjustments for haematological toxicity	Venetoclax-based regimens are associated with significant haematological toxicity. We recommend considering hospital admission for at least the first 5 days of cycle 1; it may be safer in some cases that patients remain admitted until count recovery after cycle 1. • Venetoclax should not be interrupted for haematological toxicity prior to documentation of marrow response on D21-28 • If blast clearance is confirmed and the patient has grade 4 neutropenia, G-CSF may be commenced until neutrophil recovery • Commence next cycle when neutrophil count >1 x 10^9/l and platelet count >75 x 10^9/l • If counts have not recovered above these levels by D42 a bone marrow aspirate should be performed • Once in CR, if grade 4 neutropenia or thrombocytopenia develops, cease venetoclax and commence G-CSF until resolution of grade 4 neutropenia • If grade 4 toxicity persists beyond day 42 of the previous cycle, the duration of venetoclax may be reduced to 14-21 days • If prolonged treatment-related grade 4 neutropenia or thrombocytopenia occurs in subsequent cycles, azacitidine treatment could also be reduced to 5 days

The following treatment schedule is recommended (other schedules may be used according to established local practice)	
	• In patients who have not yet been confirmed to be in CR[†], the length of treatment cycles should not be altered
Dose adjustments for non-haematological toxicity	• In patients with grade 3-4 abnormal liver function tests (i.e., ALT, AST and bilirubin), venetoclax and any potentially hepatotoxic drugs (including azole antifungals) should be withheld until these have resolved to grade 2 or below and then venetoclax (and the azole antifungal if applicable) should be restarted at the original dose • Venetoclax should not be interrupted for any other non-haematological toxicity for patients who are not in CR • In patients in CR with grade 3 or 4 non-haematological toxicity thought to be related to venetoclax, this should be withheld until the toxicity has resolved to grade 2 or below and then restarted at the original dose
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, complete response; D, day; G-CSF, granulocyte colony-stimulating factor * Please note the dose drops on D4 to account for the azole loading † Patients who do not achieve CR after cycle 2 should be discussed at a Multidisciplinary Team Meeting.	

Table 4: Emerging Targeted Therapies, Approval Status and Clinical Data Supporting Use in Elderly AML Patients

	Indication/ target	Approval status	Clinical data in elderly AML patients	References
Midostaurin	*FLT3*-mutated, newly diagnosed AML	FDA, EMA, NICE & SMC approved in combination with daunorubicin and cytarabine induction chemotherapy	In combination with intensive chemotherapy in 61-70 years age group (n=86): CR/CRi 77.9%, 2yr EFS 34% & OS 46%. In combination with azacitidine in FLT3 wildtype AML (age range 59-85; n=24): clinical response 29%, medical survival 244 days. Multiple cycles poorly tolerated.	(Schlenk*, et al* 2019)[92] (Tomlinson*, et al* 2020)[93]
Gilteritinib	F*LT3*-mutated, R/R AML	FDA, EMA, NICE & SMC approved as a single agent	ADMIRAL trial median age 62 years; hazard risk for death 0.64 for gilteritinib vs salvage chemotherapy in ≥65 year old population (n=106). Median OS 9.3 months overall.	(Perl*, et al* 2019)[22]
Quizartinib	FLT3, newly diagnosed, R/R AML	Not approved	LI-1 trial in combination with LDAC in unselected elderly AML, median age 77 yr (range 60-89; n=201); CR/CRi 16% for quizartinib +LDAC versus 10% for LDAC; no difference in OS. Monotherapy in R/R elderly (>60 years) AML population (92 *FLT3*-ITD+; 41 *FLT3*-ITD negative). CRp/CRi in FLT3-ITD+ 54%; median OS 25 weeks.	(Dennis et al, 2020)[45] (Cortes*, et al* 2019b)[94]
Sorafenib	*FLT3*-mutated, newly diagnosed	Not approved in AML. FDA approved in patients with inoperable hepatocellular cancer and advanced renal cell carcinoma	Unselected AML: In combination with 7+3 regimen in elderly fit population, median age 67 (range 61-78; n=102), no improvement in EFS or OS.	(Serve*, et al* 2013)[95]
			FLT3-mutated AML: In combination with 7+3 regimen in elderly fit population, median age 67 yr (range 60-83; n=54)– 1-year OS 62% and median OS 12.2 months.	(Uy*, et al* 2017)[96]
			FLT3-mutated AML: In combination with azacitidine in less fit elderly population; median age 74 (age range 61-86; n=27), clinical response 78%, Median OS 8.3 months.	(Ohanian*, et al* 2018)[97]
Ivosidenib	*IDH1*-mutated, newly diagnosed elderly & R/R AML	FDA approved 2018/19; not approved by EMA in 2020	FDA approval as single agent in 2019 for newly diagnosed AML in patients ≥75 years with a susceptible *IDH1* mutation and unfit for intensive therapy. This was based on trial NCT02074839 subgroup analysis; 34 patients treated, median age 76.5 years (range 64-87 years); 14/33 (42.4%) CR/CRh.	(Roboz*, et al* 2020)[98]
			Combination with azacitidine (NCT02677922): 23 patients, median age 76 years (range 61-88); ORR 78.3%; CR 60.9%, 12 month OS 82%, median OS not reached at 16 months	(DiNardo*, et al* 2021)[99]

	Indication/ target	Approval status	Clinical data in elderly AML patients	References
Enasidenib	*IDH2*-mutated, R/R AML	FDA approved 2017; not approved by EMA in 2019	Phase I/II trial as single agent in elderly unfit AML patients, median age 77 years (range 58-87; n-39). Overall response rate 31% wit CR 18%; median OS 11.3 months.	(Pollyea*, et al* 2019)[100]
Gemtuzumab ozogamicin	CD33-poisitive, newly diagnosed AML	FDA, EMA, NICE & SMC approved in combination with daunorubicin and cytarabine induction chemotherapy	Approved in combination with daunorubicin and cytarabine induction therapy for adults with good and intermediate prognosis AML based on following data: ALFA0701 – newly diagnosed AML, median age 62 years (range 50-70; n=280). No difference in CR/CRi (81% vs 75%), but improved 2-year EFS and OS (41% and 53% with addition of GO versus 17% and 42% with no GO, respectively). AML16 (UK) – newly diagnosed AML, median age 67 years (range 51-84; n=1111). No difference in CR/CRi (70% vs 68%), but reduced 3-year relapse and improved OS (68% and 25% with addition of GO versus 76% and 20% with no GO, respectively). However, in comparison, AML17 (EORTC+GIMEMA) -472 patients aged 61-75 years showed no benefit of addition of GO to treatment of older patients.	(Burnett*, et al* 2012)[101] (Castaigne*, et al* 2012)[102] (Amadori*, et al* 2013)[103]
Magrolimab	CD47	Not approved; currently in Phase 2 trials	Phase I/II clinical trial in combination with azacitidine in patients unfit for intensive treatment, median age 73 years (range 31-89; n=52 with 34 evaluable); CR/CRi 48%; median OS 12.9 months in *TP53*mutated and 18.9 months in *TP53*-wild-type.	(Sallmann *et al*, 2020)[104]
Cusatuzumab	CD70	Not approved; currently in Phase 2 trials	Phase 1 trial in combination with azacitidine in newly diagnosed elderly AML patients, median age 75 years (range 64-84; n=12). CR/CRi/CRp in 12/12 – 100%; median PFS not reached at data cut off.	(Riether*, et al* 2020)[105]
Glasdegib	Smoothened SMO	FDA approved in combination with LDAC in newly diagnosed elderly unfit AML	Randomised phase 2 trial comparing LDAC + glasdegib (n=88) vs LDAC (n=44), median age 76 years, CR 17% vs 2.3% and OS 8.8 months vs 4.9 months, respectively.	(Cortes*, et al* 2019a)[77]

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRh, complete remission with partial recovery of peripheral blood counts; Cri, complete remission with incomplete hematologic recovery; CRp, complete remission with incomplete platelet recovery; FDA, Food and Drug Administration; EFS, event-free survival; EMA, European Medicines Agency; GO, gemtuzumab ozogamicin; LDAC, low-dose cytarabine; NICE, National Institute for Health and Care Excellence; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; R/R, relative risk; SMC, Scottish Medicines Consortium

Appendix 1

Figure 1

The Edmonton Frail Scale

NAME : _____

d.o.b. : _____ **DATE : _____**

Frailty domain	Item	0 point	1 point	2 points
Cognition	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven'	No errors	Minor spacing errors	Other errors
General health status	In the past year, how many times have you been admitted to a hospital?	0	1–2	≥2
	In general, how would you describe your health?	'Excellent', 'Very good', 'Good'	'Fair'	'Poor'
Functional independence	With how many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications)	0–1	2–4	5–8
Social support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication use	Do you use five or more different prescription medications on a regular basis?	No	Yes	
	At times, do you forget to take your prescription medications?	No	Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel sad or depressed?	No	Yes	
Continence	Do you have a problem with losing control of urine when you don't want to?	No	Yes	
Functional performance	I would like you to sit in this chair with your back and arms resting. Then, when I say 'GO', please stand up and walk at a safe and comfortable pace to the mark on the floor (approximately 3 m away), return to the chair and sit down'	0–10 s	11–20 s	One of : >20 s , or patient unwilling , or requires assistance
Totals	Final score is the sum of column totals			

Scoring :
0 - 5 = Not Frail
6 - 7 = Vulnerable
8 - 9 = Mild Frailty
10-11 = Moderate Frailty
12-17 = Severe Frailty

TOTAL **/17**

Administered by : _____

Appendix 2

Figure 2

Assign scores appropriately if the recipient has any of these co-morbidities

UPN_____CIBMTR Center #_____CRID_____Date_____

Co-morbidity	Definition/compartments	Yes	Score
1. Arrhythmia	-Atrial fibrillation* -Atrial flutter* -Sick sinus syndrome* -Ventricular arrhythmia*	☐ ☐ ☐ ☐	1
2. Cardiovascular	-Coronary artery disease* -Congestive heart failure* -Myocardial infarction* -Ejection fraction ≤50%§	☐ ☐ ☐ ☐	1
3. Inflammatory bowel disease	-Crohn's disease* -Ulcerative colitis*	☐ ☐	1
4. Diabetes	-Treated with insulin or oral hypoglycemic drugs§	→	1
5. Cerebro-vascular	-Transient ischemic attacks* -Cerebro-vascular ischemic or hemorrhagic stroke*	☐ ☐	1
6. Depression/anxiety	-Requiring psychological consultation and/or specific treatments§	→	1
7. Hepatic - mild	-Chronic hepatitis§ -Bilirubin >ULN- 1.5 X ULN§ -AST/ALT >ULN- 2.5 X ULN§	☐ ☐ ☐	1
8. Obesity	-Body mass index >35 (adults)§ -Body mass index-for-age ≥95% percentile (children)§	☐ ☐	1
9. Infection	-Requiring anti-microbial treatment before, during, and after the start of conditioning§	→	1
10. Rheumatologic	-Requiring Treatment*	→	2
11. Peptic ulcer	-Confirmed by endoscopy and requiring treatment*	→	2
12. Renal	-Serum creatinine >2mg/dl (or >177µmol/L)§ -On dialysis§ -Prior renal transplantation*	☐ ☐ ☐	2
13. Pulmonary - Moderate	-DLco corrected for hemoglobin 66-80% of predicted§ -FEV1 66-80% of predicted§ -Dyspnea on slight activity§	☐ ☐ ☐	2
14. Pulmonary - Severe	-DLco corrected for hemoglobin ≤ 65% of predicted§ -FEV1 ≤ 65% of predicted§ -Dyspnea at rest or requiring oxygen therapy§	☐ ☐ ☐	3
15. Heart valve disease	-Except asymptomatic mitral valve prolapse§	→	3
16. Prior solid malignancy	-Treated with surgery, chemotherapy, and/or radiotherapy, excluding non-melanoma skin cancer*	→	3
17.Hepatic - moderate/severe	-Liver cirrhosis§ -Bilirubin > 1.5 X ULN§ -AST/ALT > 2.5 X ULN§	☐ ☐ ☐	3
		Total Score	

*Diagnosed at any time in the patient's past history

§Detected at the time of pretransplant assessment - ULN indicates upper limit of normal; DLco, diffusion capacity of carbon monoxide; FEV1, forced expiratory volume in one second; AST, aspirate aminotransferase; and ALT, alanine aminotransferase

Appendix 3

Figure 3

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.