How should we adjust treatment for older patients with haematological disorders?

Introduction

With 17% of people living in the EU now aged 65 years or older, it is becoming increasingly important that we consider whether recommended treatment approaches in oncology and haematology are appropriate for the older population. This topic was the focus of a scientific symposium held at the 15th congress of the European Hematology Association (EHA) in Barcelona in June 2010 (sponsored by Hospira UK Ltd).

The symposium was opened by Dr Matti Aapro, Dean of the Multidisciplinary Oncology Institute, Genolier, Switzerland, and Executive Director of the International Society for Geriatric Oncology (SIOG). Dr Aapro discussed the meaning of ‘old age’ and described how older patients are often under-represented in clinical trials, which has limited the scope for the development of evidence-based treatment guidelines in this patient population.1,2 His presentation highlighted the urgent need to refine practice algorithms to ensure that older patients receive optimal care.

Hairy cell leukaemia (HCL) was the focus of the next presentation, delivered by Dr Michael Grever, Chair of the Department of Internal Medicine and Professor of Internal Medicine and Pharmacology at The Ohio State University Medical Center, Columbus, USA. HCL is a chronic lymphoproliferative disorder involving a subset of B cells termed ‘hairy cells’, which have characteristic microfilamentous projections.3 Dr Grever explained how treatment options for HCL took a step forward in 1984, first with the introduction of IFN-α2a, and then with the introduction of the purine nucleosides, pentostatin and cladribine.4,5 Dr Grever reviewed the available clinical data for the treatment of HCL, which indicate complete disease remission in approximately 70–90% of patients receiving either pentostatin6–12 or cladribine.6–8,13–21 Importantly, he noted that both agents had been associated with similar long-term efficacy.6–7 With regards to patient age, Dr Grever highlighted that the median age of patients at onset of HCL is around 52 years,3 and that outcome appears to be negatively correlated with increasing age.22 However, irrespective of patient age, there are currently no internationally accepted guidelines for the treatment of HCL and Dr Grever called for the development of standardised recommendations, particularly for patients refractory to standard therapy or progressing shortly after treatment.

The faculty then considered how to manage treatment-related myelosuppression in older patients. Dr Cornelius Waller, Professor of Internal Medicine at the Freiburg University Medical Center, Germany, discussed the use of recombinant granulocyte colony-stimulating factor (G-CSF). He noted that international guidelines for...
the use of G-CSF specifically refer to age ≥65 years as a key risk factor for febrile neutropenia.23–25 Older age is also associated with an increased risk of chemotherapy-induced anaemia,26 as explained by Dr Stefan Freuehauf, Chief Haematologist/Oncologist at the Center for Tumor Diagnostics and Therapy, Paracelsus-Klinik, Osnabrück, Germany. However, Dr Freuehauf described data indicating that erythropoiesis-stimulating agents (ESAs) offer an effective therapy for anaemia, regardless of patient age.27,28 He highlighted current guidelines recommending that chemotherapy-induced anaemia in elderly patients should be managed as it is for the general population.29,30

As the Meeting Chair, I am pleased to introduce this overview of such a topical and educational symposium.

References


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How old is old age?

Due to advances in public health, modern medicine and care of older adults, the median age of the global population is increasing. Data from the United Nations indicate that for the major continents, the median age of the population has increased from 19–30 years in 1950 to 19–40 years today. By 2050, these figures are expected to reach 28–47 years. For oncologists and haematologists, these data are important as cancers may become more frequent in an ageing population. For example, UK data on colorectal cancer (CRC) show a strong association between increasing age and higher disease incidence. Approximately two-thirds of CRC patients are now over the age of 65 years. The same pattern is evident for non-Hodgkin’s lymphoma (NHL), where increasing age is coupled with increasing incidence of the disease, and approximately 70% of all new cases are diagnosed in patients >60 years of age (Figure 1).

The high incidence of solid tumours and haematological malignancies in older patients has led to a growing interest in geriatric oncology and the formation of the International Society of Geriatric Oncology (SIOG), currently led by Martine Extermann of Florida, USA. SIOG has championed research and investigation into the optimal care of geriatric oncology patients and has begun to produce its own clinical practice guidelines. This year, SIOG launched its new journal, *Journal of Geriatric Oncology*, with the aim of disseminating important new research on cancer treatment in older patients more widely.

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Older patients in clinical trials

Despite the expansion of the population of older patients with cancer, they have been under-represented in clinical trials, particularly in trials for haematological malignancies. Data from the South-West Oncology Group, one of the largest cooperative clinical trial groups in the US, indicate that most tumour types are studied in trials where less than 30% of study population is aged 65 years or older. For leukaemia, myeloma and lymphoma, patients aged 65 years or above comprise 27%, 25% and 14% of...
...age should not be a barrier to inclusion in clinical trials and access to therapy

Often-voiced assumptions that older patients may not be able to tolerate aggressive therapy may be unfounded. Literature reviews and prospectively designed trials in CRC have concluded that, in general, older patients experience similar degrees of efficacy and toxicity of chemotherapy as their younger counterparts. Many studies have evaluated standard chemotherapies in older patients with NHL. As an example, a study of a patient cohort with a median age of 66 years being treated with cyclophosphamide/doxorubicin/vindesine/prednisone (CHVP) or fludarabine/mitoxantrone (FM) therapy for NHL, showed that both regimens were well tolerated. Research such as this indicates that age alone should not be a barrier to inclusion in clinical trials; nor should it be a factor governing access to therapy in the clinic.

Optimal treatment of the older cancer patient

When making treatment decisions, we should remember that patients with cancer represent a highly heterogeneous population and that there can be variations in patient health status within older age groups. To assist in understanding the implications of these differences in patient profiles, age-related factors that should be considered when evaluating treatment options for older patients have been evaluated. These include cognition, comorbidity, emotional and physical functioning, nutrition, polypharmacy and socioeconomic conditions. Taking these elements into consideration, we should have the confidence to treat older patients with good overall health status in the same way that we treat younger patients, and adapt our approach for those with declining overall well-being.

To help us assess our older patients such that the best possible care can be given, comprehensive geriatric assessment (CGA) guides have been developed and evaluated. CGAs for geriatric assessment in cancer patients typically include many factors (Table 1), and have been used in varying formats in a number of clinical trials. These are useful clinical tools; however, the CGAs have limitations in the clinical trial setting. For instance, if a patient is being treated with adjuvant chemotherapy for breast cancer, and the CGA suggests that the patient should also receive a beta blocker, it should be considered that this additional treatment may have an impact on overall survival that could potentially skew the clinical trial results. This is still an area for development, but is one that warrants exploration.

### Table 1. Factors included in CGAs for cancer patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relevance to geriatric cancer patients</th>
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<tbody>
<tr>
<td>Comorbidity</td>
<td>Comorbidity may</td>
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<tr>
<td></td>
<td>• reduce survival</td>
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<td></td>
<td>• reduce treatment tolerance</td>
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<td></td>
<td>• reduce disease-free survival</td>
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<tr>
<td>Cognition</td>
<td>Cancer therapy can cause cognitive impairment, particularly in patients with pre-existing impairment</td>
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<tr>
<td></td>
<td>Choice of diagnostic procedure or therapeutic approach may be affected by patient cognition</td>
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<td></td>
<td>Poor patient cognition may</td>
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<td></td>
<td>• affect ability to evaluate risks and benefits of therapy</td>
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<td>• reduce compliance with treatment</td>
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<td>• affect ability to recognise signs of toxicity</td>
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<td></td>
<td>• increase time to diagnosis</td>
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<td></td>
<td>• reduce survival</td>
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<tr>
<td>Nutritional status</td>
<td>Poor nutrition is related to depression</td>
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<td></td>
<td>In the geriatric population, weight loss or low body mass index is associated with an increased risk of mortality</td>
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<td></td>
<td>Evidence suggests that older cancer survivors are more likely to be obese than non-cancer sufferers</td>
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<tr>
<td>Social support and psychological state</td>
<td>Social isolation has been shown to increase all-cause and cancer-related mortality in women with breast cancer</td>
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<tr>
<td></td>
<td>Socially isolated older adults may be particularly vulnerable to psychological distress</td>
</tr>
<tr>
<td></td>
<td>• 14–40% of older patients have depressive symptoms</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Polypharmacy can result in drug interactions and adverse events, particularly if compounded by certain physiological changes (e.g. reduced renal or hepatic function) that are common in older patients</td>
</tr>
</tbody>
</table>
Summary

The lack of clinical evidence to support geriatric use of chemotherapy results in part from a reluctance to include older patients in clinical trials. Many of the assumptions that drive this are unfounded, but, nonetheless, the clinical community is left with a situation where treating older patients can feel more like an art than a science.

Given that the population of older patients with cancer is growing, we urgently need to refine practice algorithms to ensure that this important group of patients receive optimal care. To realise this vision, we require robust clinical trial data from which to develop effective and practical assessment tools.

References


reduction and treatment delays are often considered as part of the management of FN. In studies of breast cancer and non-Hodgkin’s lymphoma (NHL), researchers have found widespread reductions in chemotherapy dose intensity versus the planned regimen. Such under-treatment may be more prevalent in older patients. Dose delays can compromise the success of chemotherapy, which is particularly important when the therapeutic intent is curative.

**Granulocyte colony-stimulating factor in the management of chemotherapy-induced neutropenia in older patients**

The risks presented by myelosuppression in commonly used chemotherapy regimens has led to the widespread use of granulocyte colony-stimulating factor (G-CSF) to reduce the risk of neutropenia and the subsequent development of FN. Current European and US guidelines recommend primary prophylaxis with G-CSF either when the risk of developing FN with a specific chemotherapy regimen is ≥20% or when it exceeds 20%. If a regimen is associated with an intermediate (10–20%) risk of FN, the guidelines recommend consideration of other risk factors. Due to the high mortality risks associated with FN, deciding which patients are candidates for primary prophylaxis and which should receive only secondary prophylaxis has led to intense study of additional patient-related risk factors beyond history of prior FN.

One of the patient-related factors that has been associated most strongly with risk of FN in response to chemotherapy is older age. The association between age and risk of FN has been demonstrated in multiple studies, primarily in women undergoing chemotherapy for breast cancer. Although the threshold for age-related risk has been found to vary between studies (60, 65 and 70 years), guidelines consider age ≥65 or >65 to be a high-risk factor for developing FN and recommend that patients in these age ranges receive primary prophylaxis with G-CSF to support delivery of high- and intermediate-risk chemotherapy regimens. The reasons that underlie the greater risk of FN in older patients are related primarily to decline in haematopoietic reserves with advancing age and the multiple comorbidities that are frequently encountered in these patients. In addition, it should be noted that comorbidities are associated with an increased mortality from FN.

...in older patients receiving chemotherapy, the response to G-CSF is preserved.

Despite the decline in circulating levels of neutrophils in older patients receiving chemotherapy, the response to G-CSF is preserved. In a study of 455 patients, aged older than 60 years, receiving cyclophosphamide, doxorubicin, vincristine and prednisonone (CHOP) or cyclophosphamide, mitoxantrone, vincristine and prednisonone (CNOP) for NHL, grade 4 granulocytopenia requiring hospitalisation occurred in 50% of patients who did not receive G-CSF, but in only 33% of patients who received the growth factor (p<0.001). In another trial of 350 older patients with NHL receiving an adapted chemotherapy regimen (cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, and prednisonone...
(VNCOP-B), the incidence of neutropenia was significantly lower in patients who received G-CSF compared with those who did not. Analyses of several clinical trials in NHL have confirmed these findings (Figure 3). Extending options for G-CSF selection

The first G-CSF to be studied and approved for use as a supportive growth factor in chemotherapy was Amgen’s Neupogen® (filgrastim). Researchers subsequently built on the success of filgrastim and were able to engineer a long-acting, polyethylene glycol (PEG)-conjugated version of filgrastim that could be used once per chemotherapy cycle. Since then, research has mainly been focussed on developing biosimilar versions of filgrastim. The approval process for European biosimilars is extremely rigorous and requires that clinical trials are conducted to prove the similarity of a biosimilar to its reference compound in terms of both efficacy and safety. Clinical trials of the biosimilar G-CSF Nivestim® (filgrastim; Hospira Inc.) have demonstrated that it is therapeutically equivalent to Neupogen. In a Phase 3 equivalence study in 37 European centres, 279 patients receiving doxorubicin and docetaxel for the treatment of breast cancer were randomised to receive supportive treatment with Neupogen (n = 95) or Nivestim (n = 184). The mean duration of severe neutropenia (DSN) in cycle 1 was similar with both agents. Importantly, the primary endpoint of the study was met since the 95% confidence interval for the difference in adjusted mean DSN in cycle 1 between Nivestim and Neupogen was within the predefined range required to demonstrate bioequivalence. In addition, the incidence of FN, the time taken for neutrophil counts to recover, and safety data were similar between the two agents. Nivestim is now approved in the Europe Union for the reduction of the duration of neutropenia and the incidence of FN in patients treated with cytotoxic chemotherapy.

Summary

In summary, older patients, particularly those with comorbidities, are at risk of developing potentially fatal FN. Prophylaxis with G-CSF can help to reduce the risk of neutropenia in this large group of patients and support the administration of potentially life-prolonging chemotherapy. Current clinical practice guidelines recommend primary prophylaxis with G-CSF in older patients, but more prospective trials are needed to ensure that patient care is optimised. New therapeutic options are now available in the G-CSF class of drugs, and these have the potential to make G-CSF therapy available to a wider range of patients undergoing chemotherapy.

Please see abbreviated prescribing information for Nivestim, located on page 12 of this supplement.
References


Assessing the needs of the older patient with anaemia

Introduction – anaemia in older adults

In older adults, anaemia is a common, multifactorial condition that can be associated with fatigue and poor quality of life. The incidence of anaemia increases with advancing age, and more than 10% of people over 65 years of age and living in the community (as opposed to in hospital or a nursing home) have anaemia as defined by the World Health Organization (haemoglobin [Hb] <12 g/dL in women and <13 g/dL in men). Prevalence increases to more than 20% in people over the age of 85 years, and is even higher in people living in nursing homes (48–63%).

Anaemia in older adults is associated with high hospitalisation rates and mortality

Anaemia in older adults is associated with high hospitalisation rates and mortality. In a community-based study of 3,607 Americans aged at least 71 years, anaemia was present in 12.5% of the population. Compared with non-anaemic patients, hospitalisation was more common in anaemic patients (65.9% versus 54.6%; p < 0.001), and anaemic patients spent more time in hospital (25.0 days versus 13.7 days; p < 0.001). A further study of 17,030 community-dwelling subjects aged ≥66 years found that Hb levels were inversely correlated with all-cause mortality, and that anaemia (Hb <110 g/L) was associated with an increased risk of hospitalisation and death. Despite the known differences in haemoregulation between men and women, mortality in both sexes is affected equally by anaemia.

Causes of anaemia in older adults

Erythropoiesis is a sensitive process and a large number of acute and chronic factors can affect it. In older patients, deficiencies in folate, iron and vitamin B₁₂ all contribute to the development of nutrient-deficient anaemia. However, blood loss via gastrointestinal lesions is generally recognised as the primary cause of anaemia in this patient group.

Older patients also suffer from progressive chronic degenerative diseases. Chronic kidney disease (CKD) is the classic chronic degenerative disease that causes anaemia. Most patients with CKD and substantially impaired renal function exhibit impaired production of erythropoietin (EPO), a critical paracrine hormone required for the generation of red blood cells from bone marrow. Recombinant human EPO (rHuEPO) and other erythropoiesis-stimulating agents (ESAs) are now established as the standard of care in patients with renal anaemia.

Despite the body of evidence that now exists to support the mechanism of anaemia in CKD and the use of ESAs to treat it, relatively few studies have been conducted to examine the relationship between CKD and anaemia in older patients. However, anaemia with renal insufficiency has been shown to account for 12.5% of cases of anaemia in patients aged ≥65 years in the USA.

Anaemia in chemotherapy – causes and treatment

Age has been identified as a risk factor for myelosuppression due to chemotherapy. In patients receiving chemotherapy, anaemia has been associated with lower survival, reduced responses to radiotherapy and increased risk of chemotherapy-induced neutropenia. For example, in a retrospective study of 605 patients with cervical cancer, the presence of anaemia (Hb <120 g/L) during radiotherapy was associated with reduced 5-year survival rates (Figure 1).

rHuEPO has been shown to be equally effective in older and younger patients

The retrospective study in patients with cervical cancer also demonstrated that the negative prognostic effects of anaemia in radiotherapy may be overcome with blood transfusions. Blood transfusions, however, are associated with risks, including ABO incompatibility due to administrative errors, transfusion-related lung injury and bacterial contamination.

In patients undergoing chemotherapy, the need for red...
blood cell transfusions can be reduced by the use of rHuEPO.11 rHuEPO has been shown to be similarly effective in older and younger patients. A 16-week community-based study of patients undergoing chemotherapy for cancer found that rHuEPO use significantly increased Hb levels to a similar level in patients aged ≥65 years and those aged <65 years (Figure 2), and reduced transfusion requirements in both groups. Both age groups also experienced significant improvements in quality of life.12

...epoetin zeta was effective in maintaining target Hb levels regardless of age...

Since the introduction of rHuEPO, clinical research in anaemia management has led to the development of a range of ESAs with differing administration regimens. Epoetin alfa and beta are both based on the genetic sequence of endogenous ePo. Genetic modifications to epoetin alfa has enabled additional sialic acid residues to be added to the native peptide, resulting in the development of the medium-acting ESA darbepoetin alfa, which can be administered once weekly or once every 2 weeks. Addition of polyethylene glycol to epoetin beta resulted in an ESA that could be administered in an ESA that could be administered once monthly.13 Biosimilar ESAs are the most recent addition to the pharmacopoeia for anaemia therapy. Epoetin zeta (Retacrit®, Hospira Inc; Silapo™, STADA Arzneimittel AG) has been studied in two Phase 3 clinical trials of patients with anaemia associated with CKD.14,15 One trial examined the correction of anaemia from a baseline Hb <9 g/dL and the other study evaluated epoetin zeta for the maintenance of Hb in the range 10.5–12.5 g/dL. In both studies, epoetin zeta was administered once to three times weekly and its efficacy and safety was compared to that of epoetin alfa. Analysis of patients aged ≤65 years compared with those aged >65 years in the maintenance study demonstrated that epoetin zeta was effective in maintaining target Hb levels regardless of age (mean Hb levels achieved: 11.4 g/dL for patients aged ≤65 years versus 11.3 g/dL for patients aged >65 years). No significant differences were seen in mean dose of epoetin zeta between age groups.16 Based on these data, epoetin zeta is now approved in the European Union for the treatment of symptomatic anaemia associated with CKD in adult and paediatric patients.17

In addition, epoetin zeta is also licensed in the European Union for the treatment of anaemia and the reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma.17 The efficacy and safety of subcutaneous epoetin zeta in patients with solid tumours and non-myeloid malignancies was studied in an open-label, single-arm phase 3 study. Analysis of data from week 12...
showed that epoetin zeta resulted in increases in mean Hb of 1.8 g/dL from baseline. By week 8, 81.5% of patients had responded to therapy (response defined as an increase in Hb ≥1 g/dL or reticulocyte count ≥40,000 cells/µL). The incidence of treatment-emergent adverse events compared well to historical data with epoetin alfa. Clinically significant thrombotic events occurred in only 4.2% of patients, which was less than the assumed 18% baseline incidence calculated from historical data.

The use of ESAs in patients undergoing chemotherapy has been a topic of debate over recent years. Certainly, caution should be exercised in prescribing these drugs to patients who have hypertension. Hypertension is an established risk factor for thrombosis. International clinical practice guidelines have recognised this and suggest that patients should be evaluated for risk of thrombosis before ESAs are used.

Summary

The global population is growing and overall we are living longer. In this older population, anaemia is a major health issue, which has been shown to negatively impact upon lives of patients, especially those with chronic kidney disease or chemotherapy-induced neutropenia. The introduction of HuEPO for the management of anaemia in patients with CKD or undergoing chemotherapy has led to the development of a range of ESAs. Available evidence suggests that appropriate use of ESAs may provide an effective and well tolerated option for the treatment of these patients.

Please see abbreviated prescribing information for Retacrit, located on page 12 of this supplement.

References
Abbreviated Prescribing Information - Retacrit Solution for Injection/Infusion, see Retacrit - 10000 International Unit/0.8 ml (4000 IU/0.4 ml): Pack of 1. EU/1/07/431/014. 8000 IU/0.8 ml: Pack of 1. EU/1/07/431/013. 6000 IU/0.6 ml: Pack of 6. EU/1/07/431/012. 4000 IU/0.4 ml: Pack of 4. EU/1/07/431/011. 2000 IU/0.2 ml: Pack of 1. EU/1/07/431/010. 1000 IU/0.3 ml: Pack of 1. EU/1/07/431/009. 6000 IU/0.6 ml: Pack of 6. EU/1/07/431/008. 40000 IU/1 ml: Pack of 1. EU/1/07/431/007. 30 000 IU/0.75 ml: Pack of 1. EU/1/07/431/006. 20000 IU/0.5 ml: Pack of 1. EU/1/07/431/005. 10 000 IU/0.3 ml: Pack of 1. EU/1/07/431/004. 5000 IU/0.2 ml: Pack of 1. EU/1/07/431/003. 2000 IU/0.1 ml: Pack of 1. EU/1/07/431/002. 1000 IU/0.05 ml: Pack of 1. EU/1/07/431/001. 500 IU/0.025 ml: Pack of 1. EU/1/07/431/000.

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Key Opinions in Medicine

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