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AKADÉMIAI KIADÓ

Anemia of geriatric patients

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ABSTRACT

Anemia is a common finding in the elderly. Approximately 10 percent of the elderly suffers from anemia. Anemia *per se* is an independent factor of mortality in older patients regardless its cause. Frailty is also frequent in geriatric patients. That means that there is a decreased reserve capacity to react to different stress factors including anemia. The frequent presence of heart failure and also impaired cerebrovascular circulation makes more difficult to tolerate anemia in older age.

Anemia is a symptom, finding and treating the underlying cause is also important.

Treatment always depends on clinical findings: the more severe the symptoms, the more important to treat them. Severity of anemia depends not only the underlying cause, degree of anemia, co-morbidities and frailty of the patients, but also the speed of its development. Sudden blood loss due to an accident is less well tolerated than the same degree of anemia due to B12 deficiency.

Main causes of anemia in the elderly include nutritional deficiencies, chronic diseases, tumors, and certain hematological malignancies such as chronic lymphocytic leukemia, multiple myeloma, myelodysplastic syndrome.

KEYWORDS

elderly, ageing, geriatric, anemia, hematological malignancies

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AGEING POPULATION

Traditionally, the "elderly" have been defined as persons of biological age of 65 years or greater, with "early elderly" going through to 74 years old, and "late elderly" including those older than 75 years of age [1]. In 2010, the elderly constituted 17.66% of the population in the European Union. This proportion increased to 20.78% by 2020 and is expected to continue rising in the coming decades. Additionally, the share of those aged 80 or older is projected to increase from 5.9 to 14.6% between 2020 and 2100. In conjunction with population aging, fertility rates of the western world have drastically decreased and this further skews society to an older distribution [2]. However, there is negligible evidence suggesting that older people today are experiencing better health in their later years than in the past. This is especially true for mild to moderate disability, where there has been little change over the past 30 years. If people were to experience a few extra years in good health, their ability to do what they enjoy and perform at these tasks will be seldom different to that of a younger person. Although, if these extra years are eclipsed by declines in physical and mental health, the implications for society and the future ageing population are negative [3]. It is therefore imperative that we change the way we think and feel towards the aging population, and to act sooner than later.

One highly prevalent condition in the elderly causing decreased quality of life and life expectancy is anemia. The World Health Organization (WHO) proposed the definition for anemia more than 50 years ago and states it occurs when the hemoglobin level falls below 130 g L^{-1} (7.5 mmol L^{-1}) in men and 120g L^{-1} (8.1 mmol L^{-1}) in women. It is important to note that these values were based on individuals who had no underlying disease and did not include subjects >65 years of age. However, these averages were justified by 3 main reasons: erythropoietin level increases to compensate for optimal oxygenation of tissues when hemoglobin level falls below this standard, the risk of surgical complications increase below this level, and hemoglobin level below this value is used as an indication for the investigation and treatment for the cause of anemia [4].

However, this standard has seen some controversy and several studies have proposed newer definitions for anemia with slight variations of hemoglobin levels. The third US National Health and Nutrition Examination Survey (NHANES) sampled an ambulatory population of 33,994 persons aged 2 months and older, with 26,372 participants receiving laboratory tests, including hemoglobin values [5]. Other studies such as the Scripps-Kaiser study [6, 7] and data from the Central Clinical Laboratory of Mayo Clinic [8] also propose differences with race, sex and age for lower limits of the haemoglobin cut-off range. In relation to the elderly, the Cardiovascular Health Study enrolled a cohort of 5,888 community-dwelling men and women aged 65 years or older, which with an 11-year follow up demonstrated that participants in the lowest quintile (<137 g L^{-1} for men; <126 g L^{-1} for women) also had an increase in mortality rate [9]. This quintile would not be classified as anemic according to the WHO criteria and was shown to be independently associated with the increased mortality, as the adjustment for the causes and symptoms of anemia not reducing the correlations seen [9]. As such, it has been suggested that the definition of anemia may be more correctly defined on the basis of a hemoglobin range correlated with the best possible health outcomes, even though this may include a greater proportion of people being classified as anemic [8]. Nonetheless, because of the inherent limitations of observational epidemiology, a causal link would require greater investigation, particularly when defining new thresholds of hemoglobin concentrations [10].

PREVALENCE OF ANEMIA

The prevalence of anemia is highly variable depending on the population studied and seems to vary between 2.9 and 61% for men and 3.3–41% in women [11]. According to the United States five National Health and Nutrition Examination Surveys (NHANES) that were analyzed every couple years from 2003 to 2012, the prevalence of anemia increased from 4.0% in 2003–2004 to 7.1% in 2011–2012 [12]. Additionally, for all age groups, blacks had the highest prevalence of anemia for both sexes and studies have found that anemia is 3.3 times more common in African Americans than in whites [13].

A systematic review of 34 studies involving 85,409 individuals demonstrated that in those aged >65 years, the prevalence of anemia was 12%, 40% and 47% in community-dwelling, hospitalized, and nursing home residents, respectively [14]. The higher rate of anemia in nursing home residents has been attributed to the poorer condition and more frequent comorbidities of elderly living in these homes when compared to those in the community [15]. Gaskell et al. [14]. additionally mentions an increase in prevalence of anemia to >25% in those aged >80 years living in the community. Comparably, a more recent study carried out by Zaninetti et al. [16]. on the prevalence of anemia of 923 admitted patients in Italy, showed that anemia was prevalent in 62% of males aged ≥65 years vs 44.1% of those aged <65 years old. Similarly, the proportion of females with anemia aged ≥65 years was 60.1% when compared to the 53.5% of those aged <65 years of age.

SYMPTOMS AND CONSEQUENCES OF ANEMIA IN THE ELDERLY

Symptoms of anemia can be divided into two main groups: general symptoms, and those related to the underlying disease.

The general symptoms of anemia may vary between individuals, yet all occur as a consequence of reduced organ oxygenation. Most commonly, fatigue is seen, though this may be accompanied by other signs such as pale skin, cold extremities, fast or irregular heartbeat, dyspnea, chest pain, headaches, dizziness, syncope and hypotension. Additionally, these symptoms could be mild and may go by unnoticed, or they may be severely debilitating. The period during which the anemia evolved is also relevant as an occult bleeding is more tolerated than rapid blood loss or an acute hemolysis. For instance, peptic ulcer disease may not present with epigastric pain in the elderly and go by unnoticed. On the other hand, general symptoms of anemia may manifest earlier in case of a young healthy adult because of the absence of comorbidities, polypharmacy and impaired organ reserves which are usually seen in the elderly.

In the elderly with coronary artery disease, anemia has been shown to worsen complaints of angina and trigger compensatory mechanisms to increase cardiac output. Such changes increase left ventricular wall stress, eventually leading to left ventricular hypertrophy [17]. Similarly, in those with congestive heart failure, the prevalence of anemia increases with the severity of disease and has been suggested as a risk factor for adverse outcomes [18]. In one study of 175 patients with chronic renal failure, every decrease in hemoglobin by 10 g L^{-1} was proportionally associated with a 6% increased risk of left ventricular hypertrophy [19]. Other comorbidities where anemia is associated with worse outcomes include cerebrovascular disease and chronic obstructive pulmonary disease [4, 20].

Even in the absence of disease, anemia has been associated with problems such as cognitive decline and dementia, frailty, increased risk of falls, decreased functional ability, depression, longer hospital stays and early mortality [10, 21]. It is also worth mentioning that these associations with anemia of the elderly remained clinically significant after controlling for possible confounder comorbidities, suggesting an independent risk of anemia on the above mentioned states [10]. Similar to the controversy of the definition of anemia and due to the inherent nature of observational studies, it is improper to assume causality and a direct pathophysiological link is yet to be discovered. Nonetheless, what can be concluded is that anemia of the elderly would still be a marker for adverse outcome and should always be taken into consideration.

Other part of the clinical symptoms beyond general ones are those associated with the underlying disease including bone pain in case of multiple myeloma, fever, loss of weight and appetite in case of malignant tumors, fever, arthralgia in case of chronic inflammation.

CAUSES OF ANEMIA

Anemia in the elderly has been classically grouped into four major categories according to the cause: 1) nutritional deficiencies; 2) chronic inflammation or disease; 3) chronic kidney disease; and 4) unexplained anemia (UA), which includes those which cannot be classified into the aforementioned categories. A fifth cause of anemia, known as clonal hematopoiesis, has been extensively studied in recent years and merits recognition, especially in the elderly.

Nutritional deficiencies

According to Guralnik et al. [22], approximately one-third of cases of anemia in the elderly are attributed to nutritional deficiencies. Iron deficiency anemia (IDA) is the most common cause of nutritional anemia and alone accounts for about half of these cases. Additional vitamin B12 (cobalamin) and folate deficiencies with an incidence of 11.4–25.3%, represent about 4.6–10.5% of anemia cases in the elderly [23].

The pathophysiology of IDA in industrialized countries is seldom due to lack of dietary supplementation and is most commonly a consequence of malabsorption or chronic blood loss from the gastrointestinal system [24]. Malabsorption causes include *Helicobacter pylori* infection, autoimmune gastritis and celiac disease whereas those due to blood loss comprise esophagitis, gastritis, peptic ulcer disease, colonic polyps, angiodysplasia, colorectal cancer, urogenital blood loss and drugs such as non-steroidal anti-inflammatories, aspirin and anticoagulants [25]. In the elderly, special consideration should be taken when considering IDA due to blood loss, as this could also signify a serious problem such as a gastrointestinal malignancy; Oesophago-gastro-duodenoscopy and colonoscopy should generally be performed to identify the source of the bleeding. In fact, in a study conducted by Joosten et al. [26]. of 151 elderly inpatients with iron deficiency, a lesion was identified in 47 from 96 patients with IDA, in which 32 were benign (gastritis, peptic ulcer disease & benign polyps) and 15 were malignancies (2 gastric cancers and 13 colonic cancers). For the remaining 55 non-anemic patients with iron deficiency, 31 patients presented with a gastrointestinal lesion; 23 benign and 8 malignancies (1 esophageal, 2 gastric and 5 colonic cancers). Similarly, in a different study where a follow-up gastrointestinal endoscopy was conducted of 100 patients with IDA, 62 had a lesion that could contribute to blood loss with 16 of those having a premalignant polyp or colon cancer [27].

B_{12} and folic acid deficiency. Anemia associated with vitamin B12 deficiency occurs primarily due to B_{12} malabsorption. This is especially true in elderly where gastrointestinal pathology and polypharmacy are more common and may alter the pharmacokinetics of B12 absorption. There are several risk factors for B12 deficiency but the most common causes are food-cobalamin malabsorption (FCM) and pernicious anemia [28]. A study of 172 elderly patients confirmed with cobalamin deficiency showed that more than 60% of patients had food-cobalamin malabsorption syndrome with pernicious anemia accounting for another 20%. Nutritional deficiency was present in only 2% and an undermined etiology represented about 10% of patients [29]. FCM is caused by an inability to release vitamin B12 from food and/or intestinal transport proteins with atrophic gastritis being the primary culprit. Other causes of FCM in elderly include chronic *H. pylori* infection, long term ingestion of antacids (proton pump inhibitors and H2 receptor antagonists) as well as metformin and chronic alcoholism [28]. An additional point of concern with B12 deficiency is that the reversibility of neurological deficits that develop prior to or in absence of hematological symptoms may only be possible in the early stages [30]. With respect to folate deficiency, the occurrence has decreased, possibly due to the fortification of flour [31], yet some causes include poor diet, chronic alcoholism, malabsorption, hemolytic anemias as well as conditions that increase cellular proliferation [32]. Use of anticonvulsants and methotrexate may also be a contributing cause [33].

Other minor causes of anemia due to nutritional deficiencies include copper and selenium. Copper deficiency leads to inhibition of the hematopoietic stem cell from maturation and division and has been reported in those receiving oral zinc supplementation [34]. Over-supplementation with zinc impairs copper absorption and hence leads to deficiency. Selenium deficiency is more commonly reported in elderly living in the community and those receiving total parenteral nutrition [21]. The mechanism of anemia due to low selenium is a result of lower glutathione peroxidase, which is important in the removal of radicals in erythrocytes.

Anemia of chronic disease/inflammation

Priory known as anemia of chronic disease, anemia of inflammation (AI) accounts for approximately 1/3 of cases of anemia in the elderly [4]. AI develops in those with chronic inflammatory conditions such as infections, chronic heart failure, diabetes, advanced atherosclerosis, malignancy, and auto-inflammatory conditions like inflammatory bowel disease and rheumatoid arthritis [23]. Additionally, the aging process is accompanied by a reduction in autophagy, as well as an increase in pro-inflammatory cytokines and reactive oxygen species which may contribute to a chronic low-grade inflammatory state, now known as 'inflammaging' [35].

There are 3 primary mechanisms of action that have been associated with AI. The first includes the inhibition of erythropoiesis, induced by the inflammatory cytokines TNF-α, IL-1 and IFN-γ. TNF-α and IL-1 expression inhibit the production and action of erythropoietin (EPO) on the erythropoietic stem cell [36]. This has been postulated to occur through GATA-2 and NF-kappa B transcription [37]. Other mechanisms downregulating erythropoietin (EPO) expression include suppression of hepatocyte nuclear factor 4 through IL-1β and secretion of microRNA 122 via TNF-α [38, 39]. Similarly, raised interferon-γ levels, such as in a chronic viral infection, reduce the expression of the erythropoietin receptor on erythropoietic precursor cells and therefore inhibits their differentiation and survival [40].

Another mechanism by which chronic inflammation induces anemia is through the expression of hepcidin. Hepcidin is an acute phase protein secreted by hepatocytes and its transcription is increased in response to activation of inflammatory cytokines such as IL-1, IL-6, IL-22 and TNF-α [41]. Other causes which have been shown to increase hepcidin levels include endoplasmic reticulum stress, formation of reactive oxygen species and reduced levels of estrogen and testosterone [33]. Hepcidin binds to the iron efflux transporter ferroportin, leading to its phosphorylation, internalization and degradation [42]. Ferroportin is responsible for the efflux of iron from the reticuloendothelial system as well as reabsorption of iron from the gastrointestinal tract [4]. In fact, about 25 mg of iron is recycled daily from senescent erythrocytes through the reticuloendothelial system [43]. This largely occurs in the splenic and hepatic macrophages and it is known that the recycling of iron stores is the primary mechanism of iron homeostasis in the human body, accounting for more than 90% of the daily iron requirements for erythropoiesis [21, 44]. As such, downregulation of ferroportin leads to the sequestration of iron intracellularly, deeming these stores inaccessible for the body and thus propagating the formation of anemia.

The third way by which chronic inflammation induces anemia is through an increase in erythrophagocytosis and reduced survival of circulating erythrocytes. Inflammatory cytokines and reactive oxygen species increase the likelihood of erythrocyte injury and eventual eryptosis. Increased reactive oxygen species can directly activate caspases and lead to cellular injury and death [21]. Other mechanisms by which eryptosis is triggered is through two signaling pathways: 1) formation of prostaglandin E2, leading to activation of Ca^{2+} permeable cation channels, and 2) phospholipase mediated release of platelet activating factor, activating sphingomyelinase and eventual formation of ceramide [36]. The increase in Ca^{2+} leads to activation of calpain and therefore precipitating cytoskeletal degradation, whilst exposure of phosphatidylserine results in opsonization and eventual phagocytosis [45]. Additionally, both TNF-α and IFN-γ have been shown to increase the expression of divalent metal transporter 1 and subsequently increase the uptake of iron in activated macrophages [23].

Unexplained anemia

Unexplained anemia (UA) represents the 'none of the above' category and occurs when patients present with normal laboratory parameters, allowing exclusion of nutritional, inflammatory and kidney related causes [10]. This particular diagnosis is more pronounced in the elderly, whereby identifying the etiology of anemia is difficult and probably multifactorial. Guralnik et al. [22] demonstrated that in elderly, UA accounts for approximately 1/3 of cases associated with anemia.

There have been several plausible theories that may account for the cases of unexplained anemia. Even in the absence of apparent kidney disease, it has been shown that the age-associated increase of EPO in those with hypertension and/or diabetes mellitus is significantly less or negligible compared to those without UA [46]. It was primarily these individuals that developed anemia during the course of the longitudinal study. Comparably, Michalak et al. [47] demonstrates that in elderly with UA, when compared to anemia of a known cause, those with UA more frequently suffer from ischemic heart disease and clopidogrel use. This relationship was assumed to be attributed to the inability to treat the anemia, hence propagating the progression of cardiovascular disease in those with UA. Michalak's study analyzed 981 patients with anemia aged 60 years or greater and additionally observed that 17% of those with UA had a prior surgery performed within 3 months before the diagnosis of anemia and suggests that hospital-

acquired anemia as being one of the main and most ignored causes of anemia in the elderly [47]. Patients whom are hospitalized often have large amounts of blood withdrawn for diagnostic purposes. In fact, hospital-acquired anemia was studied by Kurniali et al. [48], who showed that of the 479 patients that were not anemic on admission, 65% had their hemoglobin level drop by 10 g L^{-1} or more prior to discharge, with 49% of the candidates fulfilling the diagnostic criteria of anemia upon discharge. Significant results showed that a low body mass index and longer hospitalization increases the likelihood of developing hospital-acquired anemia and precaution should be taken by decreasing the frequency of blood withdrawals and perhaps using smaller volume tubes to help combat this issue [48].

Androgen deficiency is an additional factor that may account for UA. In a study of older men with mild UA and a testosterone deficiency, treatment with a testosterone gel over a 12-month period showed significant results in correcting the anemia when compared with placebo [49]. This may be a consequence of testosterone's effect to suppress hepcidin production and thus allow for increased absorption and mobilization of iron stores.

One other important, yet may be overlooked cause of anemia, especially in nursing homes is nutritional inadequacy. In a study conducted in Switzerland on 392 patients with a mean age of 85 years, 154 individuals had anemia, with 22 of those having an unspecified cause [50]. Within these patients, it was found that twenty had albumin levels lower than 35 g L^{-1}. Albeit a small sample size, low albumin, representing poor nutritional status amongst other causes, was shown to be significantly lower in anemic patients. It was concluded that undernutrition should be included in the work panel for the etiology of anemia, especially in nursing home elderly.

Low vitamin D levels has also been suggested to be a contributing cause in unexplained anemia. Susceptible elderly includes those whom may be institutionalized with frailty and reduced frequency of outdoor physical activity or with comorbidities such as chronic kidney disease which may directly influence vitamin D levels [51]. In patients with chronic kidney disease receiving hemodialysis, vitamin D repletion has been correlated with decreased requirements of erythrocyte stimulating agents in treating the anemia [52], yet more studies are required to assess the causality of this relationship.

Furthermore, it has also been suggested that a portion of UA is a consequence of low-risk or developing myelodysplastic syndrome (MDS), with this group now being classified as clonal hematopoietic disorders. Some studies have concluded that clonal hematopoiesis represents approximately 10–15% of unexplained anemia cases in the elderly. Clonal hematopoiesis will be discussed in the following section.

Clonal hematopoiesis

Clonal hematopoiesis refers to the alterations and selective mutations that occur in the hematopoietic stem cell (HSC) line. HSCs undertake multiple rounds of divisions to sustain hematopoiesis and logically are susceptible to accumulation of mutations over time [53]. The prevalence of these mutations increases and accumulates with aging, and likely provide a competitive advantage over the normal hematopoietic stem cell, potentially allowing for the development of anemia.

Idiopathic cytopenia of undetermined significance (ICUS) and idiopathic dysplasia of undetermined significance (IDUS) are potential pre-MDS conditions, characterized by cytopenic (ICUS) or non-cytopenic (IDUS) blood count, and no mutation status. Both of them might persist without progression; nevertheless, they can also develop into MDS [21].

Myelodysplastic syndrome. One of the most frequent cause of anemia among the elderly due to malignant hematological diseases are myelodysplastic syndromes (MDS). It is characterized by clonal proliferation of hematopoietic stem cells, ineffective erythropoiesis, cytopenia in the peripheral blood and a tendency to progress into acute leukemia [54].

There are two main forms of MDS according to the previous disease history: primary MDS with no previous disease and secondary MDS which is often related to prior cancer treatment.

It is a disease of the elderly indeed, as 86% of patients were aged ≥60 years at the time of diagnosis with a median age of 76 years [55].

Macrocytic anemia, elevated lactate dehydrogenase (LDH) level in the blood and fastened sedimentation rate are characteristic laboratory alterations. Bicytopenia or pancytopenia may also occur. Bone marrow aspiration is needed for detection of morphologic dysplasia and elevated rate of blast cells, while bone marrow biopsy may help to assess marrow cellularity and fibrosis. Cytogenetic examination can reveal special chromosomal abnormalities such as del(5q), +8, −7/del(7q), del(20q), and complex karyotype.

Risk stratification is extremely important for predicting the time to leukemic transformation or the risk of death from complications of cytopenia. It is based on determining the Revised International Prognostic Scoring System (IPSS-R score). Survival (in median years) for the patients of the very low risk category is 8.8 years whereas for those of being in the very high risk category is only 0.8 with a median year of 0.7 for transforming into acute myeloid leukemia (AML) [56]. Among treatment options for patients with higher-risk MDS may be allogeneic transplantation. At the time of diagnosis should be assessed including co-morbidities performance status. The upper age limit is usually around 70 years, but for fit patients it may exceed this. Other treatment options may be immunomodulating agents, erythropoietin, hypomethylating drugs besides supporting care.

Frailty and multimorbidity of geriatric patients are independent factors for poor prognosis. For these patients, supportive care with red-cell transfusions and antimicrobial drugs should be the best option as the risk of treatment-induced complications are high and improvement of the quality of life cannot be expected [57]. Being for many MDS patient the best treatment option the regularly repeated red-cell transfusion causing iron overload, the chelation treatment is extremely important.

Acute myeloid leukemia

The highest incidence of acute myeloid leukemia (AML) presents in the older adults. AML is far more common in the elderly, with a median age at diagnosis of 67 years.

Because of multimorbidity and the frequent frailty syndrome in patients of this age group treatment of the geriatric AML patients implies a great challenge. The reason of the very poor outcome in the elderly on one hand is patient-related (poor performance status, multimorbidity, intensive chemotherapy regime is not tolerated) and on the other hand it is disease-related: a different disease biology in this age group is presumed, and secondary AML (MDS transformed to AML) is more frequent.

After making a diagnosis, patients should be assessed for prognostic factors. For those few who are fit, curative therapy may be considered, such as bone marrow transplantation, whereas low intensity options may be a wise decision for frail patients.

When a patient present with profound fatigue, fever or hematomas and the laboratory data reveals anemia, thrombocytopenia and usually elevated leukocyte number (though AML can

also be manifested with low white blood cell number) a flow cytometry should be carried out from peripheral blood to diagnose AML. Bone marrow examination for histology and genetic abnormalities are important for proper classification and determination of the prognosis.

For those who are not eligible for intensive chemotherapy and stem cell transplantation, supportive therapy or low-intensity regimens (currently venetoclax-azacitidine) with supportive therapy is advised [58].

Chronic lymphoid leukemia

Chronic lymphoid leukemia (CLL) is the most prevalent leukemia in Europe and US, with a median age at diagnosis of 70 years. Usually, it becomes apparent during a screening laboratory examination showing leukocytosis, with an absolute lymphocytosis (lymphocyte number is more than 5 G/L). Most of the patients are symptomless at the time of the diagnosis. Older patients with no clinical symptoms or signs should not be treated; the recommended strategy is "watch and wait". Risk stratification should be carried out; presence of anemia, thrombocytopenia, hepatosplenomegaly, degree of lymph node enlargement, doubling time of leukocytes and clinical symptoms should be taken account. Prognostic factors include 17p deletion, unmutated IGHV status and elevated beta-2 microglobulin level. Geriatric assessment is also important for defining adequate treatment protocol. The significant improvement on the field of CLL therapy in the past decades has not resulted to much benefit for frail old patients as overall survival did not show such good results as in case of younger patients. The first real improvement concerning the therapeutic options of the elderly was ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor which acts downstream of the B-cell receptor pathway. It was successfully applied even in patients with del(17p) or TP53 (tumor protein 53) mutations for whom chemo-immunotherapy is less effective [59]. Currently the combination of bcl2 (B-cell lymphoma 2) inhibitor venetoclax with anti CD20 monoclonal antibodies and/or new BTK inhibitor can offer achieving deep molecular remission.

Multiple myeloma

Multiple myeloma (MM) is a type of lymphoproliferative disorders. It is characterized by the proliferation of malignant plasma cells that produce and secrete abnormal immunoglobulins (Igs) or Ig fragments. Typical symptoms are fatigue, loss of appetite, loss of weight, bone pain. Anemia, renal failure, hypercalcemia (altered mental status, confusion as a consequence), hyperviscosity, lytic bone lesions and an elevated plasma cell rate in the bone marrow are the most frequent findings. Sedimentation rate is usually fastened to a large extent and usually monoclonal Ig can be demonstrated in the serum and/or in the urine.

The average age of the diagnosis is of 69 years, and around two thirds of patients are over 65 years at the time of diagnosis [60].

Standard treatment for those patients who are transplant-eligible is high dose chemotherapy followed by autologous stem cell transplantation. Main aspect of eligibility for this treatment is the absence of frailty. For those who are transplant-ineligible, immunomodulating agents, proteasome inhibitors, corticosteroids are the drugs of choice. For relapsed/refractory patients, a variety of new drugs such as panobinostat, carfilzomib, elotuzumab, daratumumab, and

ixazomib may be applied [61]. Daratumumab can offer excellent results for patients over 65 years [62].

Hodgkin lymphoma (HL)

Prevalence of HL has two peaks according to the patients' age: it is most frequent in patients in their early twenties and also after age sixty. About one third of all HL patients are among the older population.

Prognosis of older HL patients is much worse than that of younger patients. This is because of several reasons including different disease biology compared with younger patients, such as increased incidence of mixed cellularity histology, Epstein-Barr virus–related, presence of B symptoms, and advanced-stage disease and also the decreased resilience of patients to chemotherapy.

Specifying treatment should be based on geriatric assessment (such as activity of daily living, cognitive status and social support). Treatment of fit older HL patients should be given with curative intent. Relapsed and refractory elderly Hodgkin lymphoma patients can mostly only be treated with the goal of palliation. At the same time, we have to pay attention for treatment-related toxicities. Because of bleomycin-induced lung toxicity, for older patients AVD (adriamycin, vinblastine and dacarbazine) may be better tolerated, than ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) [63]. Instead of agents with profound toxicity, the antibody-drug conjugate brentuximab vedotin is a very effective option with a high response rate albeit limited durability [64].

Chronic myeloproliferative neoplasms (WHO 2008) (MPN)

Median age of diagnosis of MPN is 60 years. Median age of diagnosis of MPD is 60 years with 25–50% patients over 60 years of age. Philadelphia chromosome positive (Ph+) disorder is chronic myeloid leukemia (CML) which can efficiently be treated with tyrosine kinase inhibitors. Administration of these drugs is safe in geriatric patients as well. Ph negative diseases (rare cases of CML, polycythemia rubra vera [PRV], essential thrombocytemia [ET], and myelofibrosis [MF]), hydroxyurea is still the first choice of treatment. For those ET patients when hydroxyurea proves ineffective, anagrelide can be given; it is known to be a phosphodiesterase inhibitor and mainly advised when there is an elevated risk for thrombosis. In case of PRV and ET risk stratification is a significant issue in the elderly, as patients with cardiovascular co-morbidities have a higher tendency for thrombotic complications in the first place. For these patients achieving normal erythrocyte and platelet count is especially important.

MF has reduced overall survival (OS) versus the general population. Ruxolitinib, a Janus kinase (JAK) 1 and 2 inhibitor, is a new treatment approach for intermediate-/high-risk MF. The beneficial effect on survival and mortality was recently fortified by a real-word study [65].

DIAGNOSIS OF ANEMIA

Diagnosis is based on the hemoglobin level and hematocrit value.

After establishing the presence of anemia, the underlying cause should be determined. We should always keep in mind that anemia is only a symptom (though it can *per se* be a treatable problem).

Laboratorial parameters

Anemia can be classified according to the size of the erythrocytes. Normocytic (mean cell volume is between 80–100 fL), microcytic (<80 fL) and macrocytic (>100 fL) can be determined. Value of mean cell volume (MCV) can elucidate the underlying disease. Most common causes of microcytic anemia in the elderly are iron deficiency. Macrocytic anemia in geriatric patients occurs mainly due to B12 and folate deficiency, hemolysis, hypothyroidism and myelodysplastic syndrome. Causes of normocytic anemia include anemia of chronic disease, malignant diseases, chronic renal failure, infections and bone marrow diseases.

Elevated reticulocyte count can refer to blood loss or hemolysis. We should be aware that a moderate elevation of sedimentation rate is a consequence of anemia itself.

Elevated LDH level is a frequent finding in malignancies, monoclonal protein can be demonstrated in the serum and/or in the urine of MM and Waldenström's patients.

When a low level of iron concentration is detected in the serum, ferritin (the iron storing protein) should also be measured. If ferritin level is high (being an acute phase protein) anemia might be the consequence of malignancy or chronic inflammation. The low ferritin level proves the shortage of iron (iron deficiency) due to blood loss, malabsorption or nutrition problems. In real world transferrin saturation is the most useful parameter for diagnosis of iron deficiency.

B12 deficiency can be demonstrated by measuring serum methyl-malonic acid level besides detecting a low B12 level.

Pancytopenia can refer to hematological malignancies or systemic autoimmune diseases.

Coombs' test should be indicated if there is a hint for autoimmune hemolysis.

Flow cytometric evaluation of the peripheral leukocytes, measuring the protein content and calcium level of the serum, or looking for infective agents and inflammatory parameters such as C-reactive protein (CRP) might also be necessary.

If the assumed diagnosis is a malignancy, tumor markers should be checked.

Clinical aspects of the diagnosis

There are general symptoms and signs of anemia as it was mentioned above. Fatigue, tiredness, paleness, fastened heartbeat, hypotension is typical. Jaundice is present in liver cancer, pernicious anemia, and hemolysis. General and special symptoms of malignant tumors can also be found. Neuropathy and glossitis are special signs of pernicious anemia, while cheilitis, chopped nails, and hair loss are characteristic for iron deficiency. In case of acute hemolysis, beyond jaundice, abdominal pain can occur, and it is easily misdiagnosed as acute abdominal catastrophe that require surgical intervention. If hemolysis is intravascular, urine is dark, like beer.

In case of the elderly the first clinical symptom might be confusion, sudden onset of dementia, or development of congesting heart failure.

In case of tumorous invasion of the bone marrow, infections due to leukopenia and bleeding because of thrombocytopenia.

If anemia develops slowly, symptoms are not as marked as the patient has time to accommodate to the lower erythrocyte value. If there is a sudden drop of the red blood cells (i.e., bleeding, acute hemolysis), or there is a malignant disease in the background, anemia is much less tolerated.

Imaging studies and other examinations

Imaging studies including X-ray, ultrasound, CT-scan, MRI bone scintigraphy are all important measures to identify the underlying cause of anemia and define the stage of the disease.

Bone marrow examination, gastrointestinal endoscopy, biopsy with histological examination can also be indicated.

We always should keep in mind that some diagnostic procedures can be very exhausting for old and frail patients, therefore only examinations with therapeutic consequences are indicated.

TREATMENT OF ANEMIA

Indication of treatment is the presence of clinical symptoms. The frailer the patient the more difficult to tolerate anemia. When anemia generates severe dyspnea, heart failure, or a profound impairment of brain blood circulation a fast intervention is needed. Red blood cell transfusion can quickly restore the impaired organ function. The main point, that treatment interventions should be determined according to the clinical state of the patient.

Nutritional deficiency can be restored by supplementation of the missing material (iron, vitamin B12, folic acid).

In case of MDS, or chemotherapy-induced anemia, administration of EPO is recommended.

Patients with chronic renal failure require not only regular EPO substitution, but often parenteral iron supplementation is indicated.

In case of auto-immune, or allo-immune hemolysis immunosuppression is recommended, red blood cell transfusion is not the treatment of choice. It is indicated only in life threatening situation.

Treatment of the underlying disease has upmost importance.

CONCLUSION

Anemia is very frequent in the elderly population. It affects nearly 10% of the geriatric population. The prevalence of anemia is positively correlated with the age. It is an independent factor for mortality of the aged patient. One should keep in mind that anemia is a symptom and not a discrete disease. The underlying cause should be found and treated. If anemia is severe and causes symptoms, an effort has to be made to remove it. Red blood cell transfusion is advised when the patient needs a fast restoration of the erythrocyte number because of severe clinical symptoms. Supplementation of the missing material required for erythropoiesis such as iron, vitamin B12 and folic acid is necessary. Route of administration is also important in case of the shortage of intrinsic factor in case of pernicious anemia, or if malabsorption syndrome is in the background. Older patients should be vigorously observed towards anemia because anemia has a negative impact on frailty syndrome and also, frailty can negatively influence anemia.

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