Metabolic Disorders in Elderly Patients with Hematologic Malignancies. A Review

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Abstract: Over recent decades, due to the gradual rise in life expectancy and the consequent aging of the population, the incidence of some hematological malignancies most common in the elderly is expected to increase. In elderly cancer patients, the older age is an adverse prognostic factor because of specific age-related conditions, such as changes in cellular biology and reduced functional reserve in multiple organ systems, as well as in consequence of comorbidities. Some age-related pathological conditions, such as diabetes mellitus, renal failure, chronic obstructive pulmonary disease, cardiovascular dysfunction, liver disease and other disorders may predispose the elderlies to develop metabolic abnormalities. In the elderly, the occurrence of hematological malignancies can cause some metabolic disorders or worsen pre-existing dysmetabolic conditions that increase the outcomes of these patients. Hyperuricemia is the most common metabolic abnormality; hyperuricemia less commonly may be associated with hyperkalemia, hyperphosphatemia and hypocalcemia, in the framework of oncologic emergency that is the Tumor lysis syndrome. Hypercalcemia is relatively common in patients with multiple myeloma and adult T-cell Lymphoma. Cases of Syndrome of inappropriate secretion of antidiuretic hormone *(*SIADH) in patients with hematological malignancies have also been reported. Idiopathic hyperammonemia may occur in oncohematological patients after receiving intensive chemotherapy or following bone marrow transplantation. Moreover, there is evidence that patients with lymphoma, leukemia and multiple myeloma can develop Type B lactic acidosis. Non–islet cell tumor hypoglycemia and Hyperglycemia are other potential metabolic abnormalities occurring in patients with hematological malignancies. The pathogenesis of these metabolic disorders is often unclear and several theories have been postulated; possible mechanisms include: increase in neoplastic cell turnover and apoptosis, blast crisis, cytotoxic effects of chemotherapy, tumor secretion of hormones, peptides or cytokines, immune cross-reactivity between malignant and normal tissues, malignancy-induced enzyme dysfunction. Parenteral nutrition, sarcopenia, cachexia, stress, immune deficiency and infections could contribute. Although successful treatment of the underlying tumor often improves metabolic disorders, these conditions often worse prognosis and are associated with poor survival; thus it is important to consider early detection and effective treatment.

Keywords: Hematologic malignancies, Metabolic disorders, Elderly.

INTRODUCTION

Over recent decades, due to the gradual rise in life expectancy and the consequent aging of the population, the incidence of some hematological malignancies, most common in the elderly, is expected to increase [1-3]. Actually, over the past decade, hematological malignant diseases, as Chronic B-cell lymphocytic leukemia, Multiple myeloma, Acute myeloid leukemia, Myelodysplastic syndrome and some types of Non-Hodgkin's lymphoma, have been diagnosed with increasing frequency in patients older than 65 years [4].

In elderly cancer patients, the advanced age is an adverse prognostic factor because of specific age-related conditions, such as changes in cellular biology and reduced functional reserve in multiple organ systems, as well as in consequence of comorbidities [5]. In the elderly, the occurrence of hematological malignancies can cause some metabolic disorders or worsen pre-existing dysmetabolic conditions, that increase the outcomes of these patients [6-8].

MATERIAL AND METHODS

A review of literature has been carried out via Pub Med, using the search terms hematologic malignancies in conjunction with metabolic disorders and elderly. Searches were not limited by language or human subjects. All the found items, published in the last 10 years (from July 2005 to July 2015), were analysed. Additional articles were selected from the bibliographies of the quoted references.

RESULTS

110 items were obtained: 24 case reports, 23 clinical trials (1 randomized controlled trials), 13 multicenter studies (6 comparative studies, 3 evaluation studies, 2 observational studies), 12 reviews, 1 editorial comment; the remaining items were prevalently small or short-term studies, research supports or other publication types. No meta-analysis, guidelines or consensus were found. Most of the data were deduced from retrospective analysis and by

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careful assessment of the obtained items, in particular from case reports. Hyperuricemia is the most common metabolic abnormality in patients with hematological malignancies; less commonly it may be associated with hyperkalemia, hyperphosphatemia and hypocalcemia in a framework of Tumor lysis syndrome. Hypercalcemia, Hypoglycemia and Hyperglycemia are relatively common. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), Idiopathic hyperammonemia and Type B lactic acidosis are less frequently reported.

DISCUSSION

The management of hematological malignant diseases is particularly difficult in the elderlies because these patients may have very variable health status, geriatric syndrome and comorbidities [9-11]. Some age-related pathological conditions, such as diabetes mellitus, renal failure, chronic obstructive pulmonary disease, cardiovascular dysfunction, liver disease and other disorders, may predispose the elderly patient to develop metabolic disorders [12-19]; long-term parenteral nutrition, sarcopenia, cachexia, stress, immune deficiency and infections could contribute as predisposing factors [20-25]. On the other hand, metabolic alterations are also a common feature in hematological malignant diseases. Metabolic disorders are typically detected in elderly patients after hematological malignancies diagnosis, but in some instances these alterations are manifest before tumor diagnosis; then the development of these disorders does not necessarily correlate with cancer stage. Although several metabolic disorders arise during chemotherapy or following stem cell transplantation, in many cases successful treatment of the underlying malignancy often improves metabolic disorders. Nevertheless these conditions worsen prognosis and are associated with poor survival, thus effective diagnosis and treatment of metabolic disorders may substantially improve overall clinical outcomes; for this reason it is important to consider early diagnosis and prompt treatment [7, 26-27].

This review focuses on the pathophysiologic mechanisms and diagnosis of the most common metabolic disorders in elderly patients with hematological malignancies; treatment options are also discussed.

Hyperuricemia and Tumor lysis syndrome

Hyperuricemia is a common metabolic disorder in patients with hematological malignant diseases. Uric acid is the final oxidation product of purine metabolism and increases in its plasma level can be realized in these patients by rise in neoplastic cell turnover and apoptosis, blast crisis and breakdown of malignant cells following chemotherapy, as well as it can be caused by insufficient urinary excretion [28-30]. Less commonly, as a direct consequence of neoplastic disruption, intracellular ions, nucleic acids, proteins and their metabolites are released into the plasma causing the framework of the Tumor lysis syndrome (TLS). Characteristic metabolic abnormalities of this oncologic emergency are hyperuricemia (> 8 mg/dL), hyperkalemia (> 6 mEq/dL), hyperphosphatemia (> 4, 5 mg/dL) and hypocalcemia (< 7 mg/dL) [31]. In more serious cases, large amounts of intracellular contents are released so abrupt that the normal homeostatic mechanisms are rapidly overwhelmed and TLS leads to acute renal failure and other complications as seizures, arrhythmias and sudden death [32-33]. TLS is observed most frequently in patients with Acute lymphoblastic leukemia, high-grade Lymphomas and Burkitt's lymphoma, although it may also occur in other hematologic malignancies commonly after the initiation of chemotherapy; rarely, TLS can arise spontaneously in oncohematological patients prior to the onset of chemotherapy [34, 35]. TLS is a potentially life-threatening metabolic disorder and the identification of patients at risk is essential. Vigorous hydration and anti-hyperuricemic therapy, at least 2–3 days before the initiation of cytotoxic therapy, remain the cornerstones of TLS prevention. The treatment involves intravenous hydration with approximately 3 L/m2/day and correction of acid-base imbalances; hyperkalemia, hyperphosphatemia and hypocalcemia should be treated expediently according to standard measures [32]. Hyperuricemia should be treated with Allopurinol, that prevents new uric acid formation by inhibiting xanthine oxidase, or with Rasburicase, a recombinant urate oxidase, that converts pre-existing uric acid to allantoin [30, 36, 37]. Urinary alkalinization is no longer recommended and remains controversial and the role of loop diuretics is not based on solid data, thus it should be approached on individual basis in patients at increased risk of fluid overload. Patients who have significant acute uremia, fluid overload or severe electrolyte abnormalities, should start hemodialysis as soon as possible; continuous vital signs monitoring is necessary [32].

Hypercalcemia

Multiple myeloma and adult T-cell leukemia/lymphoma are hematological malignant

diseases commonly associated with Hypercalcemia [26, 38]. Three main mechanisms can be responsible for hypercalcemia in these patients: osteolytic metastases with local release of cytokines, including osteoclasts activating factors, tumor secretion of parathyroid hormone-related protein (PTHrP), and tumor production of 1,25-dihydroxyvitamin D (calcitriol) or cytokines such as tumor necrosis factor (TNF), Interleukin 1 (IL-1) and Transforming growth factor alpha (TGF-α). Frequent clinical manifestations of malignancy related hypercalcemia are: nausea, vomiting, ileus, anorexia, dehydration, renal failure, muscle weakness, psychosis, lethargy, coma, and cardiac abnormalities as short QT interval and atrial or ventricular arrhythmia. Thus hypercalcemia may become a life threatening metabolic disorder in oncohematological patients [39, 40].

The optimal approach to hypercalcemia related to hematological malignant diseases is to treat the underlying tumor; nevertheless, fluid intravenous hydration with normal saline should be the initial treatment. The hydro-saline replenishment corrects the dehydration and increases the glomerular filtration rate. Although loop diuretics inhibit renal calcium reabsorption, these agents should not be routinely used for all hypercalcemic patients in order not to deteriorate the dehydration; these drugs may be added after adequate fluid replenishment. Intravenous Bisphosphonates are generally established as first-line therapy after volume expansion; these agents have been widely used because of inhibitory effect on bone resorption mediated by osteoclasts. Calcitonin, that inhibits bone resorption and increases the renal calcium excretion, is a useful adjunctive initial therapy. The hypocalcemic effect of calcitonin appears rapidly but it is often partial and temporary [41]. Of late, there is growing interest in the use of Denosumab, a monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANKL), in patients with bone metastases. The efficacy of Denosumab for treating malignant hypercalcemia is currently being evaluated in clinical trials [42, 43].

Hypoglycemia

There are evidences that in patients with Multiple myeloma, non-Hodgkin's lymphoma and Hodgkin's disease can occur Hypoglycemia. Production and release of insulin-like substances by cancer cells is the most recognized pathogenetic mechanism to explain hypoglycemia in these patients. Tumor cell overproduction of Insulin-like Growth Factor-2 (IGF-2), or its high-molecular-weight precursor (big IGF2), has been proven in some hematological malignant diseases, in association with consequent reduction in the blood glucose level [44-47]. Tumor oversecretion of IGF-2, or big IGF-2, is the main etiologic factor responsible for a specific clinical entity, known as Non-islet-cell tumor hypoglycemia (NICTH), that typically affects elderly patients with advanced cancer [48]. Other pathogenetic mechanisms for hypoglycemia are cancer production of autoantibodies to insulin or its receptor, Insulin-like Growth Factor-1 (IGF-1) tumor secretion and, more rarely, secretion of glucagon-like peptide-1 (GLP-1) or ectopic insulin release. In oncohematological patients, hypoglycemia may also be due to increased glucose consumption by the tumor mass and its metastases, as well as in cases with massive liver infiltration [44, 49-53]. Iatrogenic hypoglycemia has been also reported in patients treated with rituximab [54], tyrosine kinase inhibitors [55] and oral purine analogues [56], as well as in those receiving trimethoprim/sulfamethoxazole [57] and levofloxacin [58]. The exact mechanism of chemotherapy-induced hypoglycemia is not clear, while in antibiotic-associated hypoglycemia it has been suggested a sulfonylurea-like effect [57]. In non diabetic subjects hypoglycemia is usually diagnosed when venous plasma glucose is <55mg/dl in presence of symptoms, signs, or both consistent with hypoglycemia, with resolution of those after raising plasma glucose concentration. In addition to low serum glucose levels during acute episodes, NICTH is characterized by an elevated molar IGF-2:IGF-1 ratio [52].

In oncohematological patients, the optimal therapeutic approach to hypoglycemia is to treat the underlying malignancy. When it is not feasible, the aim of therapy is to maintain normal blood glucose levels. In acute hypoglycemia parenteral dextrose exerts immediate effect on blood glucose, while oral glucose administration raises glycemia in 15 to 30 minutes. For recurrent or chronic hypoglycemia, long-term management includes intravenous corticosteroids, glucagon and, in selected cases, octreotide, diazoxide or growth hormone [52, 53].

Hyperglycemia

Oncohematological patients are at high risk for Hyperglycemia because of several reasons such as prolonged glucocorticoid treatment, immune deficiency state and immunosuppressive therapy, iron overload from repeated transfusion, transplant proceedings,

frequent infections, cytokines overproduction, total parenteral nutrition, sarcopenia, cachexia, and medical stress [59]. These permanent or intercurrent factors can further worsen a pre-existing insulin resistance in patients who already have type 2 diabetes, as well as these factors can increase insulin requirement in previously normoglycemic patients. In patients with hematological malignant diseases hyperglycemia is associated with poor outcomes including increased risk of infection, comorbidities and organ dysfunction, shorter duration of remission and, in more serious cases, less eligibility for intensive chemotherapy, higher incidence of graft-versus-host disease and increased mortality [59-62]. Plasma hyperosmolality, ketoacidosis and lactic acidosis are potential life-threatening complication of severe untreated hyperglycemia [63-65] that can precipitate or worsen other metabolic disorders in elderly patients with hematological malignancy. Intravenous hydration, correction of electrolyte imbalance and pH alteration, intensive insulin therapy are the first-line treatment of acute severe hyperglycemia [66]. Oral hypoglycemic agents, unless contraindicated, alternatively could also be used to long-term control of chronic mild-moderate hyperglycemia in type 2 patients with hematological malignant diseases [67].

Type B Lactic Acidosis

Type B lactic acidosis is a rare complication of malignancy, for the first time reported in patients with Acute leukemia by Field et al [68]; since then, this metabolic disorder has been described more often in patients with hematological malignant diseases, mainly non-Hodgkin's lymphoma and Acute lymphocytic leukemia [69-72]. The exact cause of lactic acidosis in hematological malignancy remains unknown and several theories have been suggested to explain the mechanisms involved in the development of this metabolic disorder in oncohematological patients. A possible mechanisms includes an increase in the glycolytic rate in cancer cells, in part due to aberrant insulin-like growth factor signaling system that induces the overexpression of hexokinase II, the rate-limiting enzyme involved in glycolysis [73]. Moreover, in the tumor cells the avid consumption of glucose through the glycolytic pathway, even in presence of normal oxygen concentrations, causes overproduction of lactate; this metabolic process is known as aerobic glycolysis or Warburg effect [74, 75]. These mechanisms could also explain the occurrence of hypoglycemia in patients with Type B lactic acidosis, as reported in some cases of non-Hodgkin's lymphoma [45, 76, 77]. The overproduction of lactate could also be related to deficiency of thiamine that leads to pyruvate accumulation with increase in lactate production. Type B lactic acidosis can also be caused by a decreased hepatic clearance of lactate, so that oncohematological patients with extensive hepatic infiltration are at increased risk of developing this metabolic alteration. At last, the embolization of cancer cells into the microvasculature, causing tissutal hypoperfusion with increase of anaerobic metabolism, could be another possible mechanism of lactic acidosis. Type B lactic acidosis is defined as lactic acid levels above 5 mmol/L and pH less than 7,30 in whole blood [74, 78] and it can be a rapidly fatal metabolic complication if not promptly recognized and treated with emergency chemotherapy; therefore the immediate treatment of the underlying malignancy with chemotherapy is the first-line strategy [78]. Other treatment modalities include dialysis, intravenous thiamine supplementation, sodium bicarbonate infusion, and supportive management [74, 78]. However the outcome of the majority of patients with Type B lactic acidosis may be invariably fatal, suggesting that lactic acidosis may serve as marker of poor prognosis [78].

Idiopathic Hyperammonemia

Idiopathic hyperammonemia is characterized by sudden increase in blood ammonia levels with no other obvious etiology, normal liver function tests and in the absence of inborn errors of metabolism or other identifiable causes; therefore Idiopathic hyperammonemia is a diagnosis of exclusion and all other causes needs to be ruled out. This metabolic disorder is clinically characterized by neurological deterioration which mostly results in intractable coma; cerebral edema is common in these patients due to the osmotic effect of intracellular accumulation of glutamine, the major metabolite of ammonia in the brain [79]. Idiopathic hyperammonemia has been reported in some elderly patients with hematological malignant diseases [79, 80], following intensive chemotherapy [79, 81] as well as following bone marrow and stem cell transplantation [82,83]. Several chemotherapeutic agents may be responsible for this metabolic abnormality: cytarabine, daunomycin, cyclophosphamide, vincristine, etoposide, asparaginase, busulfan, and methotraxate are mainly involved; however there is some evidence of correlation between Idiopathic hyperammonemia and chemotherapy with vinorelbine, topotecan, cisplatin, rituximab, melphalan, and carboplatin. Cases of Idiopathic hyperammonemia in patients receiving

allogeneic or autologous hematopoietic stem cell transplantation are also reported [82-86]. The pathogenesis of idiopathic hyperammonemia is unclear and was hypothesized to be multifactorial. The acute elevations of ammonia and glutamine suggest acquired urea cycle defect or more general mitochondrial dysfunction induced by chemotherapeutic agents [79, 81, 84, 86]. Several hypotheses have been proposed, including chemotherapy-induced urea cycle enzymes deficiency, as carbamoyl phosphate synthetase 1, or ornithine transcarbamylase, or N-acetylglutamate synthase, and inhibition of oxidative phosphorylation complexes I and V in liver tissue. Some malignancy-related conditions, very common in oncohematological elderly patients, as sepsis and infections, particularly with urea-splitting bacteria, gastrointestinal bleeding, hyporexia, total parenteral nutrition, sarcopenia, protein catabolism and catabolic state could also contribute to hyperammonemia [86-90].

Therapeutic aim in patients with Idiopatic hyperammonemia is to correct the biochemical abnormalities and ensure adequate nutritional intake; treatment involves compounds that increase the removal of nitrogen waste. Dietary protein restriction, oral lactulose and ammonia-trapping treatment with intravenous and oral nitrogen scavengers, as sodium phenylacetate and sodium benzoate, are usually able to normalize the ammonia levels. In non-responders patients the expanded use of Carglumic acid might be warranted and intermittent hemodialysis may be requested in selected cases [91, 92].

Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)

The Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by hypo-osmotic euvolemic hyponatremia (< 134 mEq/L) and increased urine osmolality (> 100 mOsm/kg); in cancer patients this syndrome arises from tumor cell production of antidiuretic hormone (ADH), also known as arginine vasopressin, and atrial natriuretic peptide [93-94]. SIADH has been reported in patients with Large cell anaplastic lymphoma and M4 Acute myeloid leukemia [95-97], as well as after stem cells transplantation [98, 99] and during high-dose chemotherapy with some agents as cyclophosphamide and vincristine [100, 101]. The clinical signs of SIADH vary with the degree and rapidity of onset of hyponatremia, so that the patients can manifest nausea, anorexia, headache, fatigue, muscle cramps, lethargy, seizures, respiratory depression, coma [102]. The optimal therapy for oncohematological SIADH is treatment of the underlying malignancy which can normalize sodium level; other therapeutic options in correcting hyponatremia are fluid restriction (usually <1000 mL/d), intravenous hypertonic saline, adequate salt and protein intake [93, 94, 102]. Administration of vasopressin V2-receptor antagonists, as Tolvaptan, results in improvement of serum sodium levels. These drugs, which block arginine vasopressin binding to receptors in the renal ducts, act as aquaretic agents increasing the excretion of free water and retaining sodium [103]. Since 2009 vasopressin receptor antagonists can be used in many clinical situations resulting in hyponatremia, including congestive heart failure, cirrhosis and SIADH, but efficacy and safety data in cancer patients are lacking. Therefore these agents are generally considered only after failure of fluid restriction and other therapeutic options [104,105].

CONCLUSION

As consequence of age-related comorbidities, older people may have higher risk to develop metabolic disorders; in addition, a wide variety of metabolic alterations can be associated with hematological malignant diseases, increasing poor outcomes of these patients. Intensive chemotherapy and proceedings transplantation are often responsible for metabolic disorders, so that clinicians should consider these potential adverse conditions before starting standard intensive treatment protocols in these patients. Moreover, some dysmetabolic conditions are potentially life-threatening and could be serious medical emergencies. Although the immediate treatment of the underlying hematological malignancy should result in clearing of the metabolic disturbance, in several cases intensive and specific therapeutic approaches are requested. Prevention and early detection of these metabolic disorders are of crucial importance and could help improve the management of elderly oncohematological patients. In our research we have assessed 23 clinical trials, 1 randomized controlled trial and 13 multicenter studies, most of which were not designed to evaluate the metabolic outcomes of the enrolled patients. It would certainly be advisable to start prospective and observational multicenter controlled studies, aimed at giving a more accurate and actual dimension of these metabolic complications.

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