Potassium imbalances induced by systemic cancer therapy: pathophysiology and potential therapeutic strategies

ABSTRACT
Imbalances of serum potassium levels are common complications in patients receiving systemic antineoplastic therapy. These conditions can provoke further complications such as cardiac arrhythmia and paralysis due to the significant role of potassium in muscle physiology. Many cytotoxic drugs and novel targeted therapy agents have been found to induce hypokalemia and occasionally hyperkalemia. Therefore, they should be administered carefully and a broad understanding of the topic is necessary for medical oncologists. To this end, the present narrative review explores the pathophysiology of potassium disorders induced by systemic therapy and points out some therapeutic strategies for reversing them.

Key words: chemotherapy, hyperkalemia, hypokalemia, systemic therapy, targeted therapy

Introduction
Electrolyte disorders are one of the most serious and, in some cases, life-threatening medical conditions worldwide [1]. Specifically, imbalances of serum potassium (K⁺) levels, namely hyperkalemia and hypokalemia, are known to induce several serious conditions [2]. Normal serum potassium levels in adults range from 3.5 to 5.2 mmol/L, and any values out of this range are considered a pathological condition [1, 2]. Both hyperkalemia and hypokalemia, due to the significant role of potassium ions in muscular physiology, can lead to cardiac arrhythmia, muscle weakness, cramps, and even paralysis [3]. Their onset is usually sudden and can cause cardiac arrhythmia quickly, and thus they should be diagnosed and treated urgently.

Electrolyte imbalances are prevalent in patients receiving systemic cancer therapy, especially in those receiving cytotoxic drugs [4]. Although these imbalances may seldom be caused by paraneoplastic syndromes, in most cases, they are due to the effects of anticancer drugs on the cells, kidneys, and homeostasis mechanisms [5]. With potassium imbalances being one of the most serious categories of electrolyte disorders, the present narrative review aims to explore all the underlying mechanisms through which anticancer drugs induce these imbalances and present all current therapeutic strategies for reversing them.

Hypokalemia induced by systemic therapy
Hypokalemia is defined as a serum potassium level of less than 3.5 mmol/L, and in cases where the level is less than 2.5 mmol/L, the hypokalemia is categorized as severe [2, 6].
Pathophysiology

There are several mechanisms through which anticancer drugs can induce low potassium levels. Firstly, chemotherapy and some targeted therapy drugs are known to bear a risk of inducing emesis and diarrhea as major side effects [7]. Consistent vomiting and diarrheal excretions can cause excessive potassium loss through the lost body fluids [8]. Moreover, many antineoplastic agents are known to induce magnesium deficiency by binding to proteins in the nephron and decreasing magnesium reabsorption [9]. Magnesium deficiency, in turn, can lead to hypokalemia since a decrease in intracellular magnesium concentration causes inactivation of the renal outer medullary potassium channel (ROMK) and thus decreases potassium reabsorption in the thick ascending loop of Henle [10].

At the same time, many chemotherapeutic agents are known to be nephrotoxic, and, therefore, they lead to acute or even chronic kidney failure and injury as well as tubular necrosis due to cytotoxicity [11, 12]. It is worth noting that approximately 80% of patients undergoing systemic cancer therapy receive nephrotoxic agents in their therapeutic regimens [12]. During the polyuric phase of acute tubular necrosis, there is a great loss of potassium through the kidneys, and hence hypokalemia is a common complication [13].

It is also worth mentioning that antineoplastic agents have the potential to cause inflammation and necrosis in the intestinal epithelium [14]. In this manner, they can lead to reduced potassium absorption in the small intestine and thus hypokalemia [15]. Figure 1 summarizes the mechanisms through which anticancer agents can trigger the development of hypokalemia.

Specific antineoplastic agents have been shown to be related to the development of hypokalemia. Platinum-based antineoplastic drugs, namely cisplatin, carboplatin, and oxaliplatin are known to induce several electrolyte disorders including hypokalemia [16]. Cisplatin can cause hypomagnesemia by interfering with magnesium reabsorption in the loop of Henle and the distal tube of the nephron [17, 18]. It has been indicated that carboplatin and oxaliplatin can also induce hypomagnesemia, but to a lesser extent [18]. In turn, magnesium deficiency can lead to significantly decreased renal potassium reabsorption and hypokalemia [10, 16]. Moreover, unlike carboplatin and oxaliplatin, which have a great affinity for plasma proteins, cisplatin circulates freely in the plasma and is filtered to a great extent in the kidneys, and its cytotoxic nature can induce nephrotoxicity and, in some cases, acute tubular necrosis, hence leading to hypokalemia [19–21]. It is also worth mentioning that all platinum-based agents can trigger intestinal inflammation, and subsequently induce hypokalemia [22].

Antimetabolites have also been found to be associated with plunges in serum potassium levels. Indeed, the dihydrofolate reductase inhibitor methotrexate, which is included in many chemotherapy regimens, is known to increase the risk of acute kidney injury and thus that of hypokalemia [23]. Furthermore, the antimetabolite azacytidine is known to induce renal tubular dysfunction in many patients and, therefore, reduce tubular potassium reabsorption [24]. It should also be noted that the drug ifosfamide, which can act both as an alkylating agent and as an antimetabolite is associated with the development of Fanconi syndrome, which can cause both tubular dysfunction and hypokalemia [25].

At the same time, novel targeted therapy agents, which act as monoclonal antibodies, can also induce hypokalemia through the previously mentioned mechanisms. Specifically, the anti-epidermal growth factor receptor (anti-EGFR) antibodies cetuximab and panitumumab have been shown to be related to the development of magnesium deficiency and thereby lower serum potassium [26]. In fact, a meta-analysis published in 2010 indicated that the incidence of severe hypokalemia in patients receiving cetuximab in their therapeutic regimen is approximately twofold compared to patients receiving regimens without cetuximab [27]. Moreover, the monoclonal antibodies trastuzumab and pertuzumab are known to be diarrheagenic and hence increase the risk of developing hypokalemia [28]. It is worth noting that other drugs, such as irinotecan and immune checkpoint inhibitors, are known to induce chronic and severe diarrhea, hence increasing the possibility of developing hypokalemia [29]. Table 1 [17–19, 22–26, 28] summarizes all antineoplastic drugs known to increase the risk of hypokalemia, alongside the mechanism through which they induce the condition.
Management

After evaluation of biochemical blood test results, given that magnesium deficiency is identified simultaneously with hypokalemia, initially magnesium levels must be restored using oral or intravenous magnesium administration according to the standard operating procedures of the particular healthcare center [30]. Potassium replacement therapy should certainly be undertaken to restore serum potassium levels. Therapy may include oral or intravenous administration of potassium [31]. Hospitalization is not needed in cases of mild hypokalemia, where cardiac arrhythmias are not present [32]. In cases of severe hypokalemia or where the patient is unable to receive oral doses due to excessive vomiting, intravenous administration should be considered [33]. Also, it is worth mentioning that 0.9% normal saline is preferred over 5% dextrose as a solvent for intravenous therapy, as a 5% dextrose solution may induce absorption of potassium ions into the intracellular fluid [31, 34].

Hyperkalemia induced by systemic therapy

Hyperkalemia is defined as a serum potassium level of more than 5.2 mmol/L, and in cases where the level is more than 6.5 mmol/L, the hyperkalemia is categorized as severe [2, 35].

Pathophysiology

Hyperkalemia is an occasional complication in patients undergoing systemic therapy, mainly due to two reasons: tumor lysis syndrome and chronic kidney disease (CKD) [5]. The tumor lysis syndrome occurs mainly in patients with hematological malignancies or sometimes in patients with very large solid tumors, undergoing systemic therapy [36]. The latter syndrome occurs when destroyed cancerous cells release their contents into the bloodstream and since potassium concentrations are relatively high in the intracellular fluid, hyperkalemia is often induced [36, 37]. It is worth mentioning that the use of the targeted therapy drugs venetoclax, obinutuzumab, dinaciclib, and alvocidib and the use of chimeric antigen receptor T-cells (CAR-Ts) have been found to be associated with a high incidence rate of tumor lysis syndrome [38].

On the other hand, CKD can seldom occur as a long-term complication of anticancer systemic therapy [39]. In such cases, due to improper kidney function, plasma potassium excretion rates are decreased, leading to the occurrence of hyperkalemia [40]. CKD can occur in all patients receiving nephrotoxic chemotherapy, such as cisplatin and ifosfamide, over a long time [41].

Management

Generally, according to experts, initial management of hyperkalemia includes 10 mL intravenous administration of 10% calcium gluconate solution, followed by the simultaneous administration of 50 mL dextrose with 10 units of insulin and a final administration of nebulized salbutamol [42]. In the case of mild hyperkalemia where cardiac rhythm changes are not present, hospitalization is not usually required and a regimen of oral sodium polystyrene sulfonate alongside a salbutamol inhaler can be administered in an outpatient setting [42, 43]. For cases of severe hyperkalemia or when cardiac arrhythmias are present, hospitalization and the administration of calcium gluconate are deemed necessary [44]. In cases when kidney failure is not suspected, the administration of loop diuretics is not recommended [45, 46]. Otherwise, loop diuretics, such as furosemide, may be administered to reverse the hyperkalemia and hypervolemia induced by CKD, after consultation with a nephrologist [46]. Occasionally, hemodialysis may be required in patients presenting severe chronic hyperkalemia due to CKD [47].

Conclusions

As seen in this review, potassium imbalances are common complications in patients receiving systemic anticancer therapy, and due to the life-threatening

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K+ — potassium
nature of these conditions, they should be diagnosed and treated immediately. Overall, it is of paramount significance for medical oncologists to have a broad understanding of these mechanisms and underlying causes of the disorders, to choose an appropriate therapeutic strategy and to take preventive measures for patients receiving certain antineoplastic drugs.

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