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Review

Electrolyte disorders associated with the use of anticancer drugs

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ABSTRACT

The use of anticancer drugs is beneficial for patients with malignancies but is frequently associated with the occurrence of electrolyte disorders, which can be hazardous and in many cases fatal. The review presents the electrolyte abnormalities that can occur with the use of anticancer drugs and provides the related mechanisms. Platinum-containing anticancer drugs induce hypomagnesemia, hypokalemia and hypocalcemia. Moreover, platinum-containing drugs are associated with hyponatremia, especially when combined with large volumes of hypotonic fluids aiming to prevent nephrotoxicity. Alkylating agents have been linked with the occurrence of hyponatremia [due to syndrome of inappropriate antidiuretic hormone secretion (SIADH)] and Fanconi's syndrome (hypophosphatemia, aminoaciduria, hypouricemia and/or glucosuria). Vinca alkaloids are associated with hyponatremia due to SIADH. Epidermal growth factor receptor monoclonal antibody inhibitors induce hypomagnesemia, hypokalemia and hypocalcemia. Other, monoclonal antibodies, such as cixutumumab, cause hyponatremia due to SIADH. Tyrosine kinase inhibitors are linked to hyponatremia and hypophosphatemia. Mammalian target of rapamycin inhibitors induce hyponatremia (due to aldosterone resistance), hypokalemia and hypophosphatemia. Other drugs such as immunomodulators or methotrexate have been also associated with hyponatremia. The administration of estrogens at high doses, streptozocin, azacitidine and suramin may induce hypophosphatemia. Finally, the drug-related tumor lysis syndrome is associated with hyperphosphatemia, hyperkalemia and hypocalcemia. The prevention of electrolyte derangements may lead to reduction of adverse events during the administration of anticancer drugs.

Contents

1. Introduction

Drugs used for the treatment of malignancies are increasingly prescribed (Vantard et al., 2015). However, the use of anticancer drugs is associated with many side effects; among them electrolyte disturbances are relatively frequent (Ariaans et al., 2015; Filippatos et al., 2009; , 2005; Launay-Vacher et al., 2015;

Abbreviations: ADH, antidiuretic hormone; AQP-2, aquaporin-2; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; NDI, nephrogenic diabetes insipidus; PTH, parathormone; ROMK channels, renal outer medulla K^+ channels; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TRPM6, Mg^{++} transient receptor potential ion channel 6

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Miltenburg and Boogerd, 2014; Miltiadous et al., 2008; Perazella and Izzedine, 2015; Stojanovska et al., 2015; Tanvetyanon and Stiff, 2006; Teply and Lipson, 2014). In fact, electrolyte disturbances could be life-threatening if not promptly recognized and treated (Liamis et al., 2015; Miltiadous et al., 2003).

Aim of this review is to present the current evidence regarding the electrolyte abnormalities attributed to the use of anticancer drugs.

Table 1
Electrolyte disorders related to certain anticancer drugs.

Drug	Electrolyte disorder	Main mechanisms
Cisplatin and other platinum drugs	Hypomagnesemia (Lajer and Daugaard, 1999; Lam and Adelstein, 1986; Ledeganck et al., 2013; Trump and Hortvet, 1985)	Renal ± intestinal magnesium losses
	Hypokalemia (Elisaf et al., 1997; Jones and Chesney, 1995; Mohammadianpanah et al., 2004)	Renal potassium loss (usually hypomagnesemia-mediated)
	Hypocalcemia (Arany and Safirstein, 2003; Elisaf et al., 1997)	Impaired release and skeletal resistance to the action of parathormone (hypomagnesemia-mediated)
	Hyponatremia (Berghmans, 1996; Lee and Shin, 1992; Shukuya et al., 2015; Yamada et al., 2015)	SIADH and renal salt wasting
	Hypernatremia (Ready et al., 2015)	NDI
Cyclophosphamide	Hyponatremia (Gilbar et al., 2012; Park et al., 2010)	SIADH
Ifosfamide	Hypophosphatemia (Lee et al., 2001; Loebstein et al., 1999; Oberlin et al., 2009; Rossi et al., 1999)	Fanconi's syndrome
	Hyponatremia (Kirch et al., 1997)	SIADH
	Hypokalemia (Hall et al., 2014)	Renal potassium loss
Vincristine, vinblastine, vinflunine	Hyponatremia (Berghmans, 1996; Hammond et al., 2002; Raftopoulos, 2007; Ravikumar and Grage, 1983; Robertson et al., 1973; Spigel et al., 2010)	SIADH
Cetuximab, panitumumab, zalutumumab	Hypomagnesemia (Groenestege et al., 2007; Hecht et al., 2015; Muallem and Moe, 2007; Petrelli et al., 2012; Saloura et al., 2014; Wang et al., 2015)	Renal magnesium losses due to blockage of the EGF-mediated stimulation of TRPM6
	Hypokalemia (Wang et al., 2015)	Hypomagnesemia-mediated
	Hypocalcemia (Wang et al., 2015)	Hypomagnesemia-mediated
Cixutumumab, bevacizumab, icrucumab, volociximab, etaracizumab	Hyponatremia (Abou-Alfa et al., 2014; Bell-McGuinn et al., 2011; Buijs et al., 2013; Delbaldo et al., 2008; LoRusso et al., 2014; Vuky et al., 2012)	SIADH
Tremelimumab, blinatumomab	Hypokalemia (Buie et al., 2015; Chung et al., 2010; May and Glode, 2016)	Unknown
Imatinib	Hypophosphatemia (Francois et al., 2008; Osorio et al., 2007; Owen et al., 2006)	Tubulopathy-induced inappropriate phosphaturia and secondary hyperparathyroidism
Imatinib, dasatinib, nilotinib, bosutinib, axitinib, sorafenib, sunitinib	Hyponatremia (Ha et al., 2010; Hill et al., 2015; Liapis et al., 2008; Schiller et al., 2009)	SIADH
Axitinib	Hypocalcemia (Locati et al., 2014)	Unknown
Ceritinib	Hypophosphatemia (Abbas et al., 2015; Shaw and Engelman, 2014)	Unknown
Volasertib	Hypokalemia (Kobayashi et al., 2015; Machiels et al., 2015)	Unknown
Temsirolimus, everolimus	Hyponatremia (Guo et al., 2013; Javle et al., 2010; Sanchez-Fructuoso et al., 2010; Yeo et al., 2015; Zhu et al., 2011)	Aldosterone resistance
Temsirolimus	Hypokalemia, hypophosphatemia (Armstrong et al., 2013; Rodriguez-Pascual et al., 2010)	Fanconi's syndrome
Interferon, interleukin-2, levamisole, pentostatin, cytarabine, pembrolizumab, ado-trastuzamab emtansin	Hyponatremia (Berghmans, 1996; Bruno and Canada, 2007; Kolarich et al., 2014; O'Brien et al., 2012; Ribas et al., 2015)	SIADH
Ipilimumab	Hyponatremia (Barnard et al., 2012; Chodakiewitz et al., 2014; Min and Ibrahim, 2013)	Autoimmune lymphocytic hypophysitis leading to secondary adrenal insufficiency
Brivanib	Hyponatremia (Johnson et al., 2013; Shimizu et al., 2010)	Possibly SIADH
Methotrexate	Hyponatremia (Diskin et al., 2006; Frahm and von Hulst, 1988)	Toxic effect on the neurosecretory areas of the cerebrum/alteration of the distribution of body fluid volumes
	Hypokalemia (Thuss-Patience et al., 2003)	Dysfunction of ion channels on skeletomuscular membranes
Estrogens at high doses	Hypophosphatemia (Aitken et al., 1971; Citrin et al., 1984; Citrin et al., 1986; Faroqui et al., 2008).	Reduced renal phosphate reabsorption
Eribulin	Hyponatremia, hypokalemia and hypophosphatemia (Arnold et al., 2011; Koczywas et al., 2014; Morgan et al., 2015)	Unknown
Streptozocin, azacitidine and suramin	Hypophosphatemia (Izzedine et al., 2003; Kintzel, 2001; Micetich et al., 1992; Peterson et al., 1981; Rago et al., 1994)	Fanconi's syndrome
Abiraterone and orteronel [cytochrome P450 17A1 (CYP17A1) inhibitors]	Hypokalemia (Gravanis et al., 2013; Perletti et al., 2015; Shameem et al., 2015)	Suppression of cortisol synthesis leading to increase of adrenocorticotropic hormone (ACTH) and mineralocorticoids
Thalidomide	Hyperkalemia in patients with renal failure (Fakhouri et al., 2004; Harris et al., 2003; Izzedine et al., 2005; Penfield, 2006; Terrier et al., 2006)	Lysis of myeloma cells or cellular shift
Hydroxyurea	Hyperkalemia (Marusic et al., 2011)	Unknown
Drugs that cause tumor lysis syndrome	Hyperphosphatemia, hyperkalemia, and hypocalcemia (Howard et al., 2016, Locatelli and Rossi, 2005)	Lysis of malignant cells

SIADH = syndrome of inappropriate antidiuretic hormone secretion; NDI = nephrogenic diabetes insipidus; EGF = epidermal growth factor; TRPM6 = transient receptor potential ion channel 6.