JBUON 2021; 26(4): 1642-1646
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Advanced germ cell tumors and chemotherapy in G6PD deficient patients: Yes to chemotherapy but no to rasburicase and some premedications

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Summary

Purpose: *Glucose-6 phosphate dehydrogenase (G6PD) deficiency has an estimated prevalence of 5 -7.5% of the global population. Administration of some drugs in G6PD deficient patients may result in clinical conditions of varying severity, including potentially fatal sequels. For these reasons, in case of G6PD deficiency, the use of high dose toxic chemotherapy regimens in potentially curable malignancies with associated risk of tumor lysis syndrome, such as in advanced germ cell tumors, raises both physicians' preoccupations and issues for safeguard patients' health. Nonetheless no systematic information is actually available for safety in premedication to be administered, chemotherapy regimens adopted, and supportive care drugs needed to be provided in some particular situations.*

Methods: *We present a case of a patient with metastatic testicular cancer and known g6pd deficiency, admitted in our department. We also performed a literature review in tree medical libraries searching for articles addressing the overmentioned security issues.*

Results: *Available literature is particularly scant. nonetheless, there is no evidence contradicting the administration of cytotoxic chemotherapy to G6PD deficient individuals. Our patient was able to complete the preplaned chemotherapy cycles, without any complications.*

Conclusion: *Given the absence of data supporting the limitation of chemotherapy to G6PD deficient patients, the latter should not be deprived of the indicated antineoplastic treatment. However, certain premedication agents must be avoided. Continuous patient monitoring during treatment may alleviate physicians' and patients' anxiety and preoccupations.*

Key words: *testicular cancer, G6PD deficiency, chemotherapy, rasburicase, hemolysis*

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency has been recognized as the most frequent enzyme disorder, with an estimated prevalence of 5-7.5% of the global population [1]. Germ cell malignancies account for 1-2% of malignant neoplasms affecting the global male population [2], being more frequently diagnosed among adolescents and young men [3].

Although there is no reported association between testicular cancer and G6PD deficiency [4], due to their prevalence in the overall population, co-presence of G6PD-deficiency and advanced tes-

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Received: 12/02/2021; Accepted: 08/03/2021

ticular cancer may occur, arising the therapeutic dilemmas for the safety of chemotherapy administration in G6PD deficient patients.

The impressive cure rates of advanced testicular cancer are indeed achieved by the administration cytotoxic chemotherapy [5]. According to the degree of G6PD insufficiency administration of some drugs in G6PD deficient patients may result in different severity clinical condition including potentially fatal hemolytic anemia, permanent neurological damage, icterus, hypoxia, and methemoglobinemia [6-9] (for this reasons WHO classified G6PD deficiency in five categories (Table 1).

Nonetheless, there is no sufficient evidence suggesting that antineoplastic agents may provoke G6PD deficiency related clinical sequelae, with only few case reports of G6PD deficient patients with testicular cancer receiving chemotherapy [4, 10]. We thereafter revised the summarized relevant literature and report a case of advanced recurrent seminoma in a G6PD deficient patient who successfully received 3 BEP (bleomycin, etoposide, cisplatin) cycles.

Case description

A 40-year-old patient, with known G6PD deficiency, but otherwise insignificant medical history, palpated a nodule in his left testicle, in July 2019. The scrotal MRI showed a suspicious mass, while his LDH was 249 U/L, with beta HCG and AFP within the normal range. He underwent left orchiectomy, revealing a pure seminoma, 5.6 cm in maximal diameter, without infiltration of lymph or blood vessels, the epididymis, the tunica vaginalis or the spermatic tone, with negative excision margins (stage pT1b). His full body CT scan was negative for secondary sites. In September 2019, he received one cycle of adjuvant carboplatin (800mg, AUC 6) in the oncologic department of the University Hospital of Ioannina. Subsequent CT scans during the follow up showed no evidence of metastatic disease up to June 2020. Unfortunately, in December 2020, our patient presented with enlarged retroperitoneal lymph nodes (maximal diameter 2.9cm) with high glucose absorption rate in the PET/CT scan, confirming suspicion of metastatic disease. Precautiously, chemotherapy was administered on an inpatient basis, in order to constantly monitor his red blood cell count, hemoglobin and bilirubin levels, looking for hemolysis indications. The patient demonstrated excellent tolerance, with a stable hemoglobin concentration around 13-14g/dl, completing all 3 cycles of the selected regimen, up to February 2021.

Literature review

PubMed, ResearchGate and ISI Web of Science were screened for relevant literature.

1. *Chemotherapy regimen:* Overall only three G6PD deficient patients who had been treated for testicular cancer were reported in the literature [4, 10, present case]. Both BEP (bleomycin, etopo-

Table 1. G6PD classification by WHO (World Health Organization, 1989)

Class I	Severely impaired	chronic non-spherocytic haemolytic anaemia (CNSHA)
Class II	Less than 10% of normal	intermittent hemolysis
Class III	10-60% of normal	hemolysis only if triggered
Class IV	60-150% of normal	asymptomatic
Class V	Increased activity	asymptomatic

Table 2. G6PD patients who received chemotherapy for testicular or extragonadal germ cell carcinomas

Patient	*neoplasm*	*Disease extent*	*Agents*	*G6PD level*	*Complications*	*Reference*
40 yo male	Pure seminoma	retroperitoneal lymph nodes	BEPx3 cy	Not counted	none	present
26 yo male	Testicular embryonal carcinoma	Lung metastases, retroperitoneal lymph nodes	BEP x 4 cy	33.1mU/ 10^9 erythrocytes (n.r.>118mU/10^9 erythrocytes)	DVT	Uema et al, 2018
74 yo male	Testicular embryonal carcinoma	retroperitoneal lymph nodes causing obstructive jaundice	VIP x 1 cy	Not reported	Pneumonia, septic shock, death	Schmidt et al., 2010

Table 3. Hemolysis triggered in individuals with G6PD defficiency (Harcke 2019, WHO 1989)

Antimalarials	Primaquine, pamaquine, hydroxychloroquine
Drugs	
Sulphonamides and sulphones	Sulfamethoxazole-trimethopsrin, sulfonylureas, sulphanilamide, sulphapyridine, sulphadimidine, sulphacetemide, acetyl sulfisoxazole, salazopyrin, sulphoxone, glucosulphone sodium
Nitrofurans	Nitrofurantoin, furazolidone, nitrofurazone, nalidixic acid, chloramephenicol, p-aminosalicylic acid, phenazopyridine
Nitric acid	Nitroglycerine, sodium nitropusside
Analgesics	Aspirin, acetophenetidin- but paracetamol is low risk
Anthelminthics	β-naphtol, niridazole, stibophan
Antimycobacterials	Isoniazide, dapsone
Antibiotics	Ciprofloxacin, moxifloxaxin, levofloxacin, streptomycin
Vitamins	Vitamin K analogues, high-dose vitamin C
Anti-uric acid	Rasburicase, probenecid, Colchicine
Antihistamines	Dimentindene, Diphenydramine, Hydroxyzine
Miscellaneous	toluidine blue, methylen blue, mepacrine, dimecaprol
Other substances	Napthalene, arsine, henna
Foods	Fava beans
Viral/bacterial infections	cytomegalovirus, hepatitis A and B, pneumonia, typhoid fever

Important note: The above list is strictly indicative-for up to date information about substances contradicted in G6PD deficiency, please visit https://www.uptodate.com/, https://www.fda.gov/, https://www.g6pd.org/en/G6PDDeficiency/SafeUnsafe.aspx

side, cisplatin) and VIP (ifosfamide, etoposide, cisplatin) regimens were safely administered without triggering a G6PD dependent hemolytic crisis (Table 2). Nonetheless, some amendments concerning supportive medications of VIP and TIP (paclitaxel, ifosfamide, cisplatin) regimens are made in the supportive care paragraph.

2. *Premedication:* Use of antihistaminic drug in the context of premedication is officially contradicted by the relevant health organizations (Table 3). Importantly, rasburicase, an agent usually employed against tumor lysis syndrome, which is not an infrequent complication of testicular cancer treatment, has been reported several times to induce hemolytic anemia and/or metheglobinemia in undiagnosed G6PD deficient males [11-15]. Rasburicase premedication in G6PD deficient patients should be thereafter avoided. Considering that elevated tumor burden is a frequent event in advanced germ cell tumors, G6PD pre-testing before rasburicase administration in preventing tumor lysis syndrome has been suggested [16].
3. *Supportive care:* Analgesics, antihistaminic and some antimicrobials are officially contradicted by the relevant health organizations (Table 2).

Importantly, it should be considered that ifosfamide (frequently used in salvage treatment regimens such as TIP or VIP, after testicular cancer relapse), can cause ifosfamide-induced metabolic encephalopathy, with symptoms ranging from mild symptoms such as acute confusion to non-convulsive seizures, severe irreversible coma, and death. Methylene blue, a contraindicated drug for G6PD deficient patients (Table 3), is widely used in treating ifosfamide-induced metabolic encephalopathy in every-day clinical practice, although its efficacy is not well established. For this reason, physicians administering VIP or TIP regimens in a G6PD deficient patient should be aware about methylene blue potential sequels. Nonetheless, it should be also referred that methylene blue was successfully administered in two patients with ifosfamide-induced metabolic encephalopathy with cutaneous T-Cell lymphoma without triggering G6PD deficiency crisis. Thereafter, the use of methylene blue to treat ifosfamide-induced metabolic encephalopathy should be very cautious and limited to patients with more severe symptomatology, balancing both the potential risk and benefits for its administration [17].

Discussion

Overall, the reported literature was particularly scant both for number of reports and relative consistency.

G6PD deficiency is a common enzymopathy, leading to hemolytic crisis under certain triggers, including pharmaceutical and non-pharmaceutical substances. Despite their ability to induce oxidative stress, chemotherapy agents have not been shown to cause any clinical sequelae in G6PD deficient patients with germ cell malignancies. Some premedication drugs such as antihistaminic and rasburicase (for preventing tumor lysis syndrome) should be not administered. In relapsed patients treated with ifosfamide-based regimens (such as VIP or TP), and experiencing ifosfamide-induced metabolic encephalopathy, the use of methylene blue (a drug contraindicated in G6PD deficient patients) should be extremely cautious and after a meticulous balancing of the risks and benefits for its use and the particular clinical condition of the patient.

Consequently, G6PD deficient patients suffering from germ cell malignancies, should not be deprived of the appropriate cytotoxic chemotherapy, while careful monitoring during treatment will reassure their well-being.

Clinicians should also mindfully consult the lists of agents incompatible with G6PD deficiency, even before prescribing commonly employed supportive medications.

There is a need of more methodical reporting of G6PD deficient oncologic patients receiving antineoplastic agents (chemotherapy, immunotherapy, targeted agents), as well as a wider application of G6PD prescreening before antineoplastic treatment initiation, aiming to both safeguard patients' health and respond to physicians' preoccupations.

Conflict of interests

The authors declare no conflict of interests.

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