Novel Insights from Clinical Practice

Oncology Research and Treatment

Oncol Res Treat 2019;42:350–353
DOI: 10.1159/000497216

Received: October 26, 2018
Accepted: January 23, 2019
Published online: April 17, 2019

A Different Kind of Relapse: Ethanol as an Additive in Chemotherapy Formulations

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Established Facts

- Many chemotherapy formulations contain ethanol as a solvent.
- During infusions of ethanol-based chemotherapy blood alcohol concentrations can rise noticeably.
- Ethanol-induced side effects in chemotherapies can occur.
- Standard informed consent forms and guidelines typically do not address this matter.

Novel Insights

- We report on a patient with a history of previous alcohol abuse who experienced a relapse after a single infusion of docetaxel.
- Physicians should be aware of this potential risk of ethanol-based chemotherapies, especially when treating vulnerable patients.
- Patients should be informed about expected risks and benefits and advised on potential alcohol-free alternatives.

Keywords
Addiction · Chemotherapy · Complication management · Ethanol · Ethics · Informed consent

Abstract
Some chemotherapy formulations contain ethanol as a solvent which can become relevant for medical and nonmedical reasons. Only a few studies have tried to quantify the effects of ethanol in chemotherapy preparations. Furthermore, the alcohol amount highly depends on the specific formulation, with some variation among different manufacturers. Although the actual increase in blood alcohol levels after ethanol-based chemotherapies seems to be limited, the FDA recently released a warning that docetaxel may cause symptoms of alcohol intoxication. Here, we report on a patient with breast cancer who experienced a relapse of alcohol abuse after a single docetaxel infusion. We hypothesize a causal relationship with the ethanol-containing docetaxel infusion. Today, no guidelines exist for the use of ethanol-based chemotherapy, and patient consent forms do not address this matter. We conclude that physicians pre-

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scribing chemotherapy and patients should be aware of the potential risks of ethanol-containing infusions and nonethanol-based alternatives should be discussed when needed or desired by the patient. This could be facilitated by revised patient consent forms.

Introduction

Despite recent advances in targeted therapies, highly lipophilic chemotherapy formulations remain some of the most effective and widely used substances in contemporary oncology. To facilitate intravenous (IV) administration some preparations typically contain ethanol as a solvent. This is the case for most of the taxanes, including paclitaxel, docetaxel, and cabazitaxel. As ethanol-containing chemotherapy is administered IV, the central nervous system is confronted with unmetabolized alcohol. Studies could show a rise in blood alcohol levels up to 0.27‰ after paclitaxel infusion (175 mg/m^2) which, depending on local legislation and age of the patient, would make it illegal to operate a vehicle [1, 2]. When administered over the course of 3 h the elimination rate of alcohol may approximate the infusion rate, resulting in relatively low levels in most patients with a normal liver function [3]. While acute alcohol intoxication may not be a widespread problem, there have been some reports of patients experiencing symptoms of alcohol intoxication after receiving paclitaxel [4] and a new formulation of docetaxel which contains more alcohol than its predecessor [5]. This eventually led the US Food and Drug Administration (FDA) to issue a warning in 2014 that some chemotherapy infusions may cause symptoms of alcohol intoxication after treatment [6].

Ethanol-based medications might also be harmful in more ways than acute intoxication. The amount of alcohol administered IV during an infusion of paclitaxel for a patient with ovarian cancer and a body surface of 1.72 m^2 amounts to 19.25 g of ethanol. That is roughly equivalent to one large glass containing 500 mL beer (5% alcohol by volume). Even minor amounts of alcohol are suspected to potentially trigger a relapse of alcohol abuse in patients suffering from alcohol addiction. According to a review of Seo and Sinha [7] in 2014, a relapse of alcohol abuse may be caused by an onset of compulsive *craving*, an intense urge to resume drinking when confronted with certain risk factors. These risk factors include alcohol, so-called alcohol cues (which can be visual, olfactory, or auditory), or stressful live events. German guidelines for prescribing oral medications [8] require physicians to check for alcohol-free alternatives whenever they plan to prescribe alcoholic formulations to vulnerable patients (including children and patients suffering from liver disease or alcohol addiction). No such national guidelines exist for prescribing IV medication, though. The possible number of patients at risk is high: according to a survey *(Alkoholatlas)* of the German Cancer Research Centre, in 2017 approximately 1.3 million people living in Germany could be defined as alcohol dependent [9]. According to the National Survey on Drug Use and Health in 2016 in the USA, an estimated 15.1 million people aged 12 or older had an alcohol use disorder [10].

Case Report

We present the case of a 64-year-old woman who was diagnosed with breast cancer and liver metastases, UICC stage IV, cT2, pN1a, M1 (HEP) G2. The cancer subtype was found to be ER/PR negative, with an HER2 score 3+ and a KI67 proliferation index of 20%. The history of the patient included alcohol abuse leading to a Child-Pugh class A liver cirrhosis. At the time of breast cancer diagnosis, the patient had been abstinent from alcohol for 7 years. Her attending gynecologist initiated a palliative treatment with docetaxel and trastuzumab/pertuzumab. After the first chemotherapy infusion further treatment had to be canceled as the patient was committed to the psychiatry ward because of a relapse of her alcohol addiction. We were asked for an oncologic consultation and hypothesized that the ethanol-based infusion of docetaxel had potentially caused or at least contributed to the relapse of alcohol abuse. After being released from the psychiatric ward the patient discontinued treatment and was unfortunately lost for follow-up. It remained unclear whether the patient had been properly informed about the alcohol content of the chemotherapy. Yet a review of the preprinted consent forms commonly used for information about IV chemotherapy in our hospital revealed that none of them mention the fact that some chemotherapy formulations contain alcohol.

Results

The available data so far suggest that IV alcohol in chemotherapy formulations does not confer a major risk for most patients. However, for patients with a history of alcohol addiction there is a risk of provoking a relapse of alcohol abuse. This risk can be aggravated when combined with an abnormal liver function, like in our patient who had liver metastases and cirrhosis. Another important contributing risk factor can be psychological stress. Being confronted with the bad news of incurable cancer diagnosis certainly qualifies as a major stressful life event that may provoke a relapse of alcohol abuse. We conclude that patients with an increased risk should be informed about the alcoholic formulations and possible alternatives to make an informed decision.

While this information seems to be evident for medical reasons it can also be relevant for patients without such medical risk factors. A person who wishes to abstain from alcohol for religious reasons for example might also need

Table 1. Ethanol as an additive in some widely used chemotherapy formulations

Usually free of ethanol	nab-paclitaxel, 5-fluorouracil, carboplatin, cisplatin, cyclophosphamide, doxorubicin, epirubicin, pemetrexed, topotecan
May contain larger quantities of ethanol, depending on product	paclitaxel, docetaxel, cabazitaxel, gemcitabine, etoposide

this information to make an informed decision. These patients might weigh the risk of foregoing an effective ethanol-based treatment for a less proven nonethanol-based treatment differently than their physicians might expect. For the sake of patient autonomy, this should be considered.

Discussion/Conclusion

The case we presented highlights possible side effects of specific chemotherapy formulations that are often overlooked because they are caused not by the main ingredient, but by an additive solvent. There have been other case reports that detailed intoxication symptoms after chemotherapy infusions, but none that point to the specific risk of contributing to a relapse of alcohol abuse. The implications from this case have some limitations. First and foremost, we cannot prove whether the relapse of alcohol abuse was directly caused by the exposure to alcohol in the context of chemotherapy. It is highly probable that the psychological stress of an incurable cancer diagnosis was at least a contributing factor, as was the patient's abnormal liver function. It seems warrantable that oncologists know about these specific risk constellations and properly inform patients who are at risk by exposure to alcohol or may wish to avoid alcohol intake for other personal or religious reasons. Informed consent as the legal and bioethical prerequisite to any invasive medical procedure is only appropriate when patients are fully informed about their specific risks and benefits. In some cases, it may be justified to offer alternative therapy regimes that are alcohol free but may not be as effective in reaching remission. After reviewing various summaries of product characteristics for widely used IV chemotherapy formulations we found the amount of ethanol to differ between substances and specific products (Table 1). While docetaxel formulations for example typically contain ethanol, the FDA has recently approved a new formulation of docetaxel that was specifically developed as an alcohol-free alternative [11].

It remains to be discussed whether preprinted consent forms should include the fact that some chemotherapy formulations contain alcohol. These forms are not supposed to cover all possible risks for every patient. It is the physician's obligation to weigh the benefits and risks of the specific formulation for the specific patient. On the other hand, preprinted forms can support the patient and the physician in identifying risks that matter most to the patient. Even more so when it comes to nonmedical reasons for abstaining from alcohol, transparent and effective patient information may not only be legally and bioethically required but will also prove beneficial for a sustainable physician-patient relationship.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources relevant to this article to declare.

Author Contributions

Hansjakob Fries was the main author of the article. Marcus Hitzschke was consulting oncologist in the case presented and co-authored the article. Florian Lordick supervised and co-authored the article.

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