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Impact of hyperglycemia on the efficacy of chemotherapy—A systematic review of preclinical studies

Maaike C. Gerards[a,*], Daphne L. van der Velden[b], Joke W. Baars[b], Dees P.M. Brandjes[a], Joost B.L. Hoekstra[c], Titia M. Vriesendorp[d], Victor E.A. Gerdes[a]

[a] MC Slotervaart, Amsterdam, The Netherlands
[b] Antoni van Leeuwenhoek Hospital/Dutch Cancer Institute, Amsterdam, The Netherlands
[c] Academic Medical Center, Amsterdam, The Netherlands
[d] Isala, Zwolle, The Netherlands

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ABSTRACT

Background: Antineoplastic agents can provoke hyperglycemia in cancer patients with and without diabetes mellitus. We systematically reviewed the impact of hyperglycemia on the efficacy of chemotherapy.
Methods: MEDLINE was searched for preclinical intervention studies which compared chemotherapy response in hyperglycemic and euglycemic conditions.
Results: Thirteen preclinical studies, including 23 cell lines and 2 animal experiments were identified. In 14 cell lines and 2 animal studies, chemotherapy response was lower in a hyperglycemic (>15 mmol/L) compared to a euglycemic environment (5 mmol/L). The response was similar in 4 cell lines. In the remaining 5 cell lines, the hyperglycemic environment potentiated chemotherapy efficacy.
Conclusion: Hyperglycemia attenuated the antiproliferative effect of chemotherapy in preclinical experiments, but the results are inconsistent. Whether hyperglycemia influences efficacy of chemotherapy in patients needs to be explored.

1. Introduction

Patients with diabetes mellitus or impaired glucose tolerance (IGT) frequently experience severe hyperglycemia during antineoplastic chemotherapy. Various antineoplastic agents, including glucocorticoid therapy, cisplatin, everolimus, docetaxel and

* Corresponding author at: MC Slotervaart, Louwesweg 6, 1066 EC Amsterdam, The Netherlands.
E-mail address: m.c.gerards@amc.uva.nl (M.C. Gerards).

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androgen deprivation therapy can contribute to uncontrolled hyperglycemia (Ariaans et al., 2015).

Diabetes mellitus has been associated with an increased risk of chemotoxicity and also with an increased mortality rate in cancer patients (Barone et al., 2008; Brunello et al., 2011). This association may be explained by hyperglycemia being an epiphenomenon of impaired general condition and comorbid disease and associated higher mortality risk (Marik and Bellomo, 2013). Also, organ dysfunction associated with diabetes mellitus (nephropathy, polyneuropathy, vasculopathy) has impact on the dosages of chemotherapy tolerated by the patients and risk of toxicity (Zanders et al., 2013). An alternative explanation for the increased mortality in patients with diabetes, is that chemotherapy is less effective in patients with diabetes mellitus and a hyperglycemic tumor environment.

If there is a causal relationship between hyperglycemia and an impaired response to chemotherapy, intensive glucose lowering therapy might improve treatment outcomes in patients with diabetes and IGT and might even improve survival.

In this study, we systematically review the evidence on the effect of hyperglycemia on outcomes of antineoplastic chemotherapy with respect to survival and proliferation of malignant cells in preclinical studies.

2. Methods

2.1. Literature search

We performed a systematic review with a narrative synthesis of results. The protocol was published online (http://www.crd.york.ac.uk/prospero, CRD42015025179). We included studies in which the response of cancer to chemotherapy was compared between a hyperglycemic and a euglycemic environment. MEDLINE was searched (January 1980–December 2015) for index terms as well as text words, limited to English language publications as shown in table S1. The first reviewer (MG) identified potentially eligible studies based on title and abstract and the selection process was verified by the second reviewer (DV). Since only one clinical study was eligible, we chose to include preclinical studies only.

2.2. Data collection and extraction

Data were extracted independently on standardized data extraction forms by the 1st and 2nd reviewer and disagreements were resolved through discussion. Reviewers collected data on study design and methods including glycemic intervention and co-interventions, population characteristics, outcomes regarding direction of effect and mechanistic pathway, and methodological quality. Methodological quality studies was assessed by the SYRCLE bias tool for preclinical studies (Hooijmans et al., 2014).

2.3. Data synthesis

An overview of findings is presented with an explanation on the findings for the different types of cancer and chemotherapy modalities.

3. Results

The search strategy retrieved 5299 results of which 13 met the selection criteria (Fig. S1) (Bhattacharya et al., 2014; Biernacka et al., 2013; da Silva Faria et al., 2015; Friday et al., 2011; Garufi and D'Orazi, 2014; Ma et al., 2014; Vishvakarma et al., 2013; Zeng et al., 2010; Zielinska et al., 2015; Feng et al., 2011; Pandey et al., 2011; Turturro et al., 2007; Yu et al., 2015).

Table 1
Mice studies.

Cancer type	Organ	Glucose condition		Chemotherapy		Survival in HG condition	Control without chemoRx	Hypothesized mechanism
		HG (mM)	NG (mM)	Agent	Dose			
Dalton lymphoma (Vishvakarma et al., 2013)	Lymphoma	Supplement 0.75 g/kg	Ascitic fluid	Methotrexate Cisplatin	2 mg/kg	–	Yes, =/–	↑ Glucose utilization in later tumor stage (through ↑ GLUT-1 expression) and HG influences cell survival regulatory molecules.
Sarcoma 180 (da Silva Faria et al., 2015)	Sarcoma	>13,8 mmol/L	Physiological	Cisplatin	20 mg/kg	–	Yes, =	Renal excretion of cisplatin is increased in DM

Results of mice studies. Results of preclinical studies. Outcome is indicated as: – (less survival in hyperglycemic condition), = (no difference in survival), + (better survival in hyperglycemic condition). *Abbreviations*: GLUT-1 = glucose uptake transporter 1. HG = hyperglycemia. NG = euglycemia.