Short term fasting, IGF/insulin-axis and therapy outcome in patients with cancer

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Chapter 1

General introduction and outline

Introduction

Effective approaches of prevention, diagnosis and treatment of cancer are necessary as cancer is the second leading contributor to mortality worldwide after cardiovascular diseases and its incidence is still increasing[1]. The obesity epidemic is one of the explanations of the increasing incidence and mortality due to cancer[2] and increasing our understanding of its relation with cancer may lead to more effective treatment of cancer.

Long-term caloric restriction without malnutrition decreases cancer incidence and mortality in non-human primates[3]. Moreover, short periods of fasting improve cancer treatment outcome in rodents[4] and may be feasible in humans as an addition to cancer treatment[5]. However, research in humans is in its infancy and the exact mechanism and effects are not established yet.

Short-term fasting as an adjunct to cancer treatment

Short-term fasting (STF) protects rodents from toxic effects of chemotherapy, radiotherapy and targeted therapy, while enhancing the efficacy of the cancer therapy in distinct malignancies[6,7]. This distinct response of healthy versus cancer cells to periods of nutrient deprivation is called differential stress resistance (DSR). Healthy cells are protected during starvation due to activation of nutrient sensing pathways. These pathways are highly preserved between species[8,9] and regulate that healthy cells invest energy in repair and maintenance rather than growth[10,11]. For example, autophagy (Greek for "self-eating") is a conserved catabolic process among eukaryotes to survive periods of nutrient deprivation[12].

In contrast, cancer cells are unable to slow down growth due to mutations in tumor suppressor genes and mitogenic pathways and may be more vulnerable during periods of starvation[7,12]. Moreover, declines of plasma levels of insulin like growth factor-1 (IGF-1), insulin and glucose are among the mediators of the effects of fasting on cancer cells[13,14].

Therefore, short-term fasting is a promising strategy in humans to increase tolerability and efficacy of cancer treatment[15], at least in non-cachectic patients. However, so far no randomized data on efficacy were available. Besides, it is unknown for which human tumors short-term fasting could be effective and what the optimal timing and duration of the fasting and refeeding should be. Additionally, some difficulties need to be addressed as how to increase compliance in patients: though as promising as STF seems, it puts additional burden on the patient. Perhaps, to ease the burden of fasting a fasting mimicking diet (FMD) may be an alternative to increase compliance, as it mimics the effects of short-term fasting on metabolism[16]. Another difficulty that needs to be addressed is how to introduce short-term fasting in treatment regimens with

corticosteroids. These agents are commonly used in chemotherapy schedules and may interfere with the benefits of short-term fasting due to hyperglycemia induction.

IGF-1 and insulin in cancer

Insulin-like growth factor 1 (IGF-1) and insulin are members of the IGF-1 pathway, which is involved in cell growth and proliferation by activation of the Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K)/AKT pathways[17]. Elevated levels of IGF-1 and insulin, due to obesity or diabetes mellitus for example[18], have been associated with development, progression, metastasis and worse survival of cancer[14]. IGF-1 and insulin activate the IGF-1 receptor (IGF-1R) and the insulin receptor isoform A (IR-A), which are both frequently upregulated in distinct types of cancer[19].

IGF-1R inhibitors, which are highly effective in preclinical studies, did not show convincing benefits in clinical studies[20]. One of the explanations of these disappointing results might be that IGF-1R inhibition causes upregulation of the ligands due to abrogation of negative feedback in the pituitary. To overcome this resistance to IGF-1R inhibitors in humans short-term fasting may be the key solution as insulin and IGF-1 decrease dramatically during fasting[13].

Outline

This thesis focusses on the effects of short-term fasting and the IGF-1 and insulin pathway on toxicity and efficacy of chemotherapy in patients with cancer.

Outline of this thesis

Part I. **Short-term fasting and fasting mimicking diets as an adjunct to cancer treatment**

The subject of Part 1 of the thesis is further introduced in a review article (**Chapter 2**) on the effects of short-term fasting on cancer treatment. The current knowledge of the molecular mechanisms explaining differential stress resistance (DSR) of healthy versus cancer cells in response to fasting are described. Additionally, the available (ongoing) clinical data reflecting the impact of short-term fasting on the effects of chemotherapy in cancer patients are summarized and critically reviewed.

The subsequent chapters describe clinical trials of short-term fasting in patients with breast cancer. A randomized-controlled pilot trial (NCT01304251) was performed to identify the effects of 48-hours of short-term fasting on chemotherapy-induced side effects in patients with breast cancer, who received docetaxel, doxorubicin and cyclophosphamide (TAC) chemotherapy **(Chapter 3)**. A subsequent study, the

multicentre, randomized, phase II/III DIRECT study (NCT02126449) evaluated the impact of a fasting mimicking diet (FMD) on toxicity and efficacy of chemotherapy in patients with breast cancer **(Chapter 4)**. The aim of these two clinical studies was to evaluate the feasibility of short-term fasting/FMD in patients with cancer. Furthermore, these studies explored the effects of short-term fasting/FMD on growth factors, such as IGF-1, insulin and glucose, and the effects of fasting on DNA damage in healthy cells. The main goal was to evaluate the effects of fasting/FMD on toxicity and efficacy on standard chemotherapy.

***Part II*. IGF-1 and insulin pathway in cancer treatment**

In Part II of this thesis, the effects of the IGF-1 pathway on chemotherapy outcome and the pathway itself as target for cancer therapy are described. In **Chapter 5** the current knowledge of IGF-1R inhibitors for treatment of cancer and hypotheses to overcome the resistance mechanisms to these inhibitors are reviewed, supported with preclinical data. Ewing sarcoma, a rare cancer localized in the skeleton or soft-tissue, is used as a simple model, as the IGF-1 pathway may play a major part in its pathogenesis[21]. In the subsequent chapters tissue of the breast cancer patient cohort of the NEOZOTAC trial (NCT01099436) is used to evaluate the expression of the IGF-1R of the tumor before and after neoadjuvant chemotherapy and whether it predicts pathological response according to the Miller and Payne classification after neoadjuvant chemotherapy. Furthermore, the aim was to identify single nucleotide polymorphisms (SNPs), which have been described to influence the activity of the IGF-1 pathway, to predict chemotherapy efficacy and toxicity in this cohort (**Chapter 6**). In **Chapter 7** the same cohort is used for translational research of the IGF-1 pathway in patients with breast cancer, where associations between IGF-1R expression and serum levels of IGF-1 and insulin, and survival are examined. The last study of this thesis evaluates whether circulating levels of IGF-1 and IGF-binding protein 3 (IGF-BP3) can predict the (event-free) survival of patients with Ewing sarcoma treated with vincristine/ifosfamide/doxorubicin/etoposide (VIDE) chemotherapy **(Chapter 8)**. Finally, the thesis is concluded with a summary, general discussion and future recommendations.

References

1. Global Burden of Disease Cancer C, Fitzmaurice C, Abate D, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol.* 2019.
2. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body Fatness and Cancer--Viewpoint of the IARC Working Group. *N Engl J Med.* 2016;375(8):794-798.
3. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science.* 2009;325(5937):201-204.
4. Safdie F, Brandhorst S, Wei M, et al. Fasting enhances the response of glioma to chemo- and radiotherapy. *PLoS. One.* 2012;7(9):e44603.
5. Safdie FM, Dorff T, Quinn D, et al. Fasting and cancer treatment in humans: A case series report. *Aging (Albany. NY).* 2009;1(12):988-1007.
6. Raffaghello L, Lee C, Safdie FM, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. *Proc. Natl. Acad. Sci. U. S. A.* 2008;105(24):8215-8220.
7. Lee C, Raffaghello L, Brandhorst S, et al. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. *Sci Transl Med.* 2012;4(124):124ra127.
8. Ruetenik A, Barrientos A. Dietary restriction, mitochondrial function and aging: from yeast to humans. *Biochim Biophys Acta.* 2015;1847(11):1434-1447.
9. Lee C, Longo VD. Fasting vs dietary restriction in cellular protection and cancer treatment: from model organisms to patients. *Oncogene.* 2011;30(30):3305-3316.
10. Fontana L, Partridge L, Longo VD. Extending healthy life span--from yeast to humans. *Science.* 2010;328(5976):321-326.
11. Bishop NA, Guarente L. Genetic links between diet and lifespan: shared mechanisms from yeast to humans. *Nat. Rev. Genet.* 2007;8(11):835-844.
12. van Niekerk G, Hattingh SM, Engelbrecht AM. Enhanced Therapeutic Efficacy in Cancer Patients by Short-term Fasting: The Autophagy Connection. *Front Oncol.* 2016;6:242.
13. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. *Endocr. Rev.* 1994;15(1):80-101.
14. Pollak M. Insulin, insulin-like growth factors and neoplasia. *Best Pract Res Clin Endocrinol Metab.* 2008;22(4):625-638.
15. de Groot S, Pijl H, van der Hoeven JJM, Kroep JR. Effects of short-term fasting on cancer treatment. *J Exp Clin Cancer Res.* 2019;38(1):209.
16. Brandhorst S, Choi IY, Wei M, et al. A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan. *Cell Metab.* 2015;22(1):86-99.
17. Zhu C, Qi X, Chen Y, Sun B, Dai Y, Gu Y. PI3K/Akt and MAPK/ERK1/2 signaling pathways are involved in IGF-1-induced VEGF-C upregulation in breast cancer. *J Cancer Res Clin Oncol.* 2011;137(11):1587-1594.

18. Garcia-Jimenez C, Gutierrez-Salmeron M, Chocarro-Calvo A, Garcia-Martinez JM, Castano A, De la Vieja A. From obesity to diabetes and cancer: epidemiological links and role of therapies. *Br J Cancer.* 2016;114(7):716-722.
19. Belfiore A, Malaguarnera R, Vella V, et al. Insulin Receptor Isoforms in Physiology and Disease: An Updated View. *Endocr Rev.* 2017;38(5):379-431.
20. Yee D. Insulin-like growth factor receptor inhibitors: baby or the bathwater? *J Natl Cancer Inst.* 2012;104(13):975-981.
21. Benini S, Zuntini M, Manara MC, et al. Insulin-like growth factor binding protein 3 as an anticancer molecule in Ewing's sarcoma. *Int.J.Cancer.* 2006;119(5):1039-1046.