Diazoxide for Lowering Insulin Levels in Breast Cancer Patients

Ferroni et al. described pretreatment insulin levels as a prognostic factor for breast cancer and suggested interventions targeting glucose metabolism with metformin to improve survival of these patients [1]. We recently reviewed this topic [2] and agree with this approach, but we believe that diazoxide should also be mentioned in this context.

Diazoxide is a nondiuretic benzothiadiazine that produces hyperglycemia by lowering insulin levels through activation of ATP-sensitive K+-channels and stimulating insulin degradation in the lysosomal system. With a dose of 300 mg per day, diazoxide has been shown capable of markedly decreasing fasting and glucose-stimulated insulin levels in healthy subjects, as well as decreasing IGF-1 levels in polycystic ovary syndrome patients [2].

The effect of diazoxide on cancer growth was first examined in DMBA-induced mammary carcinomas of the rat [3]. In a nontoxic dose, diazoxide led to a remission rate of 82%. After cessation of diazoxide treatment due to progression, 30% rebound responses were observed in animals that had a first remission; this rebound response is characteristic of hormonal therapy. In MNU-induced mammary carcinomas, treatment with 300 mg/kg diazoxide per day induced a remission in 55% of the animals. This effect was completely abolished by additional treatment with 2 IU depot insulin per day, and, thus, an insulin-mediated effect of diazoxide was proven [3]. Adding 200 mg/kg diazoxide synergistically prolonged the remission duration induced by different tamoxifen doses by about 50% [2].

In a clinical pilot study with nine breast cancer patients, diazoxide was used at a dose of 200–300 mg per day [4]. For inclusion, maximal tolerated fasting glucose level was 110 mg/dL, and 180 mg/dL after an oral glucose load with 75 g. The best response was seen in a 60-year-old woman, who had glucose levels of only 56–105–115 mg/dL in the oral glucose load test. After progression of her cutaneous metastases during tamoxifen treatment, she was supplemented with 200 mg diazoxide per day and her fasting glucose levels rose to 90 mg/dL. Partial remission with this combination ended after 7 months when liver metastases were detected sonographically. Two months later, both medicaments were withdrawn because of rapidly growing cutaneous metastases and pleural effusion. Another 2 months later, the patient exhibited a rebound response of 4 months duration with the disappearance of pleural effusions, partial remission of the cutaneous metastases, and stable size of the liver metastases. In two additional patients with prior disease progress, diazoxide treatment resulted in stable disease of 8 (combined with tamoxifen) and 4 (monotherapy) months [4].

We think that diazoxide is an underrated drug for studies on cancer treatment because it lowers insulin and IGF-1 levels. While hyperglycemia correlates with poor outcomes in cancer patients [2], this side effect could be overcome by combining the drug with (a) acarbose, which completely inhibited mammary carcinogenesis in rats [5]; (b) carbohydrate restriction, which by itself could retard tumor growth [6]; and (c) medium chain triglycerides and exogenous ketone bodies, which rapidly elevate ketone body levels while decreasing blood glucose concentration [7]. Such combinations could have the potential to prolong tamoxifen-induced remissions markedly.

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Disclosures
The authors indicated no financial relationships.

References

1. Ferroni P, Riondino S, Laudisi A et al. Pretreatment insulin levels as a prognostic factor for breast cancer progression. ***The Oncologist*** 2016;21:1041–1049.

2. Klement RJ, Fink MK. Dietary and pharmacological modification of the insulin/IGF-1 system: Exploiting the full repertoire against cancer. Oncogenesis 2016;5:e193.

3. Berger MR, Fink M, Feichter GE et al. Effects of diazoxide-induced reversible diabetes on chemically induced autochthonous mammary carcinomas in Sprague-Dawley rats. Int J Cancer 1985;35:395–401.

4. Fink M, Abenhardt W, Ostermayr B et al. Insulin and diazoxide for treatment of cancer: Results of clinical pilot studies. Onkologie 1991;14:158–164.

5. Schlüter G. Toxicology of acarbose, with special reference to long-term carcinogenicity studies. In: Creutzfeldt W, ed. Acarbose for the Treatment of Diabetes Mellitus. Berlin: Springer, 1988:5–16.

6. Klement RJ, Champ CE, Otto C et al. Anti-tumor effects of ketogenic diets in mice: A meta-analysis. PLoS One 2016;11(5):e0155050.

7. Kesl SL, Poff AM, Ward NP et al. Effects of exogenous ketone supplementation on blood ketone, glucose, triglyceride, and lipoprotein levels in Sprague-Dawley rats. Nutr Metab (Lond) 2016;13:9.

http://dx.doi.org/10.1634/theoncologist.2016-0402