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Clinical usage of hypolipidemic and antidiabetic drugs in the prevention and treatment of cancer

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Abstract

Factors predisposing hormone-dependent tissues to the development of tumors coincide, at least partly, with hormonal-metabolic promoters (like insulin resistance, glucose intolerance, visceral obesity, etc.) of other main non-communicable diseases. This important knowledge poses the question of whether the same approach which is applied for prevention/treatment of a metabolic syndrome and the associated endocrine disorders might also be used in preventive and therapeutic oncology. Whereas an answer to this question remains controversial and is based mainly on experimental evidence, there is accumulating clinical data suggesting a practical significance of such a strategy, even though it is not to be considered as directly cytostatic. Among the many drugs under discussion, three groups of medicines (statins, antidiabetic biguanides, and thiazolidinediones) are the most attractive. The concept of metabolic rehabilitation is proposed and used practically in an adjuvant setting for the correction of the above-mentioned endocrine-metabolic disorders commonly found in cancer patients. The current use and aim of this approach is to improve the survival of patients and limit cancer progression. Nonetheless, it also appears potentially useful as a neoadjuvant therapy as well as a prophylactic treatment earlier in life for specific groups of people with hormone-associated enhanced oncological risk. It seems possible that certain hypolipidemic and antidiabetic medicines with pleiotropic effects might be combined with traditional antisteroid prevention/therapeutic approaches in routine clinical situations as well as for overcoming resistance to standard cancer hormonal therapies including receptor-negative cases. Characteristic at the end of the 20th and at the beginning of the 21st century is an epidemic of diabetes and obesity, which might further increase the incidence of certain cancers. This makes it timely to apply hypolipidemic and antidiabetic drugs (in combination with reasonable dieting, increased physical fitness, and an in-depth knowledge of drug-gene interactions) as an approach warranting further study.

Keywords: Hormone-dependent tumors; Insulin resistance; Obesity; Dyslipidemia; Statins; Thiazolidinediones; Biguanides; Fibrates; Proliferation; Differentiation; Apoptosis; Prevention; Treatment

1. Introduction

Science frequently goes in cycles. The subject that will be discussed in this paper is no exception. There have been several attempts based mainly on

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experimental observations to study the effect of hypolipidemic and antidiabetic drugs as possible anticarcinogenics. The arguments were established some time ago [1–4]. This was followed by a period of relative indifference, which was described in recent *Journal of National Cancer Institute* editorial. The authors stated that, 'The whole area of metabolism in cancer has been neglected in the last 30–40 years' [5]. The recent interest in this area, belonging according to terminology used in mentioned article [5] and in some other publications to the so called 'metabolomics,' is in reality associated with more serious and far reaching considerations. Basically, there appears to be common, or partially common, hormonal-metabolic mechanisms leading to development of major non-communicable human diseases [6–8]. Taking into account data that have been accumulated lately and the experience of our laboratory in this field, headed for a long time by the late Prof. Vladimir Dilman [7,9,10], it is warranted to discuss the problem reflected in the title of this paper. We will concentrate deliberately on clinical aspects of the problem making the discussion as balanced as possible.

2. Why hypolipidemics and antidiabetics and which ones?

The reasons for the possible usefulness of hypolipidemic and antidiabetic medicines in the prevention and treatment of cancer can be characterized briefly as historical, hormone(metabolism)-related and cell function-related. Besides, it should be added that—as it will be demonstrated below—a rather large part of the clinical data in the so-called preventive area with rather rare exception was collected, if you will, unintentionally, that is, not as a result of planned and randomized anticancer research.

More than 70 years ago it was stated that cholesterol excess was an oncological risk factor and such statements led to the conclusion that restriction of this excess was needed [11]. However, the problem of 'cholesterol and cancer' is multifactorial and multipolar, and only one of its sides is related to the role of cholesterolemia in cancer. For two consecutive decades, in the 1980s and 1990s, the point of view on danger of the 'low blood cholesterol' prevailed [12]. This was recollected when the carcinogenicity of some lipid-lowering drugs in rodents was discussed [13]. Later it was demonstrated that preexisting cancer might be responsible for the low cholesterol 'phenomenon', and contemporary long-term prospective observations often (although not unanimously) could not find any relation of cholesterolemia to cancer morbidity/mortality or showed a U-shaped relationship [14,15]. In relation to the mentioned carcinogenicity of certain classes of lipid-lowering substances in rodents, the majority of the most popular opinion nowadays states that extrapolating results observed in this species to man is fraught with many hazards. Among others the following limitations have to be taken into account: (a) the difference in drug disposition, metabolism and (most importantly!) sensitivity to its action, (b) the difference in doses used, and (c) the high spontaneous rate of cancer in rodents [16].

Gradually, interest in the 'cholesterol and cancer' problem shifted from cholesterolemia to the cholesterol biosynthesis in malignant cells and to the role of cholesterol in cell membranes [17–19]. The latter, together with additional data, served as an explanation for the involvement of cholesterol in key cellular processes and functions throughout the whole body. Reparation of such functions now is considered an important aim of the use of hypolipidemics in oncology. Besides, it partly determines the choice of these drugs whereby preference is given to the inhibitors of cholesterol biosynthesis, which limit proliferation, and to the substances that increase cellular differentiation and apoptosis (see 'Section 3').

Probably the most important reason for the ever rising interest in the possible antiblastomogenic effects of hypolipidemics and antidiabetics is due to contemporary views elucidating how age- and lifestyle-associated changes in endocrine homeostasis increase the risk of hormone-dependent cancer. This emerging view provides for the situation(s) predisposing individuals to simultaneous development of most frequent, and eventually lethal, chronic human pathologies and contends with the similarities and differences between hormonal-metabolic pathways leading to their formation. According to the data accumulated for hormonal disorders to date, special attention is paid to the phenomenon of hyperinsulinemia/insulin resistance, which presents an important part of the so-called metabolic syndrome. Typical characteristics of this syndrome include hyperinsulinemia, impaired