

The Therapeutic Effect of Statins on Survival of Patients with Gastrointestinal Cancer: a Review

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ABSTRACT

Cancer can significantly have ruining effects on very high of human beings, social, and economic condition. Gastrointestinal (GI) cancer has been reported as one of the most prevalent cancers and the incidence rates of this disorder is increasing across the world. This review explains practical recommendations for the management and improvement of patients with GI cancer by statins. Statins, a group of lipoproteins drugs, are used in medicine to treatment of lipid disorder, hypercholesterolemia reduction and cardiovascular risk. The exact mechanisms of anticancer activity of statins are still unknown. However, in some preclinical and epidemiological studies have reported them to have anticancer properties and therapeutic consequences for GI cancer based on preclinical evidence of their including antihypoxic processes, anti-invasive, induction of growth arrest and proapoptotic, radiosensitizing, angiogenesis and inhibition metastasis. The main objectives of this review paper are: 1. Explain the importance of sickness understanding and prognostic awareness in patients with cell proliferation, induction cell apoptosis, metastasis, angiogenesis, immunity and inflammatory GI cancers receiving statins groups. 2. Explain the importance of statins therapy in low- and middle- risk patients with GI cancers.

Key words: Cancer, Gastrointestinal, Statins, Adjuvant therapy.

Abbreviations used:

GI = (gastrointestinal)

EC = (esophageal cancer)

CRC = (colorectal cancer)

HUVEC = (human umbilical vein endothelial cell)

Introduction

Gastrointestinal (GI) cancer (including esophageal cancer (EC), gastric cancer and colorectal cancer (CRC)) has been reported as one of the most common cancers in all over the world. Although statins are broadly used to treat the GI cancer, but their

mechanisms are still unknown. Most of the current published data have focused on statins as chemopreventive agents, but there is increasing interest in its use for treatment of GI cancer. Most suspected patients with GI cancer show advanced disorders to palliative management.

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors-HMG-CoA reductase inhibitors) is commonly used to treat the primarily raised cholesterol, dyslipidemias and cardiovascular disease in certain patients after surgery, chemotherapy and radiation therapy. They are known to have low side effects in clinical uses; suggesting low-side effects (Lee *et al.*, 2014).

In turn, this medication (timing, dosage, and duration of statins therapy) can block and reduce the growth of cancer cells and promote cell survival, by interfering in inhibition of tumor cell proliferation, induction of proapoptotic, angiogenesis, immunomodulatory and inhibition metastasis in the all tissue types and cancer cell lines (Table 1). Thus we hypothesized that suspected patients who were appointed to statins treatment (especially long-term and high therapeutic concentrations) would have protective effects on GI tumor or related cancer.

This comprehensive review evaluates the complex interaction among statins therapy, improved survival and decreased morality rates in patients with GI tumor or related cancer, we next explain the importance of sickness understanding and prognostic awareness patients with GI cancer.

Table 1. Key studies describing the comprehensive anti-cancer effects of statins (as a multiple functions drugs) on gastrointestinal

Inhibition of tumor cell proliferation	Kureishi <i>et al.</i> (2); Kato <i>et al.</i> (3); Cheng-Qian <i>et al.</i> (4)
Induction of cell apoptosis	Agarwal <i>et al.</i> (5); Ogunwobi and Beales, (6); Spampanato <i>et al.</i> (7); De Llobet <i>et al.</i> (8)
Proangiogenic (Low-dose)	Weis <i>et al.</i> (9); Assmus <i>et al.</i> (10); Spyridopoulos <i>et al.</i> (11)
Angiogenesis	Chylack <i>et al.</i> (12); Fildes <i>et al.</i> (13)
Neurodegeneration (medium-dose)	
Angiostatic (high-dose)	Lee <i>et al.</i> (1)
Inhibition of metastasis	Lee <i>et al.</i> (1); Demierre <i>et al.</i> (14)
Inflammatory and Immunity	Fildes <i>et al.</i> (13); Pahan, (15); Poggi <i>et al.</i> (16); Diakos <i>et al.</i> (17)
Antioxidant activity	Fildes <i>et al.</i> (13), Farmer, (18); LaRosa, (19)

Treatment goals of statins on gastrointestinal cancer:

Each section of the part of this review explains short statements, the key practical recommendations related to the section of therapeutic benefit of statins on GI cancer, followed a summary of the supporting new research documents.

Inhibition of HMG-CoA reductase by the statins may be attributed to rate-limiting step of the *L*-mevalonate pathway (necessary pathway to synthesis of cholesterol and protein prenylation) and also vital pathway for a various row of end products (such as geranylgeranyl pyrophosphate and farnesyl pyrophosphate)), make reduced levels of *L*-mevalonate and its downstream products that most of these product and pathway play important roles in critical cellular functions (Ras and Ras homologue) including

membrane integrity, cell signaling (dividing cancer cells need necessary cholesterol for synthesis of cell membranes), protein synthesis (proteins are essential for regulate cell cycle, invasion, proliferation, and migration), and cell cycle progression (Chan *et al.*, 2006, Pisanti *et al.*, 2014). With regards to effect of statins on post-transcriptional modifications of oncoproteins ad Ras and Rho, the anti-tumour effect of statins has been accepted in various cancer cell lines (Kim *et al.*, 2001, Park *et al.*, 2000, Lee *et al.*, 2006).

In trust, the improper expression of HMG-CoA reductase could be contributed to tumorigenesis schedule in GI cancer. Subsequently, control of *L*-mevalonate pathway in GI cancer cells by the statins therapy can proceeding better regulation of tumor growth, angiogenesis and metastasis, thus, statins therapy could have positive significant influences on many vital cellular functions in GI cancer. To summarize, statins therapy does seem to improve survival and decrease morality rates in patients with GI cancer.

Inhibition of tumor cell proliferation

The permanent cross-talk between cancer cells are essential for tumor growth, tumor necrosis, incursion, inflammation, angiogenesis, and tumor metastatic spread. The antineoplastic impacts of statins have also been shown in human gastric cancer cell lines by decreased cell division on total transcriptome microarrays (Cheng-Qian *et al.*, 2014), by inhibiting the synthesis of cholesterol and proteins protein prenylation. Also, (Cheng-Qian *et al.*, 2014) have indicated that statins prevented the growth rate of GI cancer cells, also the weight and volume of tumours in animal, thus, chemotherapy drugs may interact with the effect of statins therapy (Wang *et al.*, 2002). Therefore, statins treatment interfering with molecular action and reaction involved in cell signaling secretion and cell viability, and finally statins therapy could inhibit tumor cell proliferation in GI cancer.

Induction cell apoptosis

Several international studies in the field of cancer research (especially those with a stem cell or basic science focus) have indicated that induction of cell apoptosis is a one of well-established marker of suitable prognosis in many cancers. A new known mechanism is that statin drugs can interfere in gastric tract cancer and provoke apoptosis rate of GI cancer cells, and prevent angiogenesis or target mechanisms implicated in the metastatic spread of cancer (Cheng-Qian *et al.*, 2014), by interfering in the rate-limiting step of the *L*-mevalonate pathway. A recent clinical experiments has indicated that the induction of apoptosis process in breast cancer cell lines with Simvastatin was associated to the enhanced pro-apoptotic BAX coupled to the decreased anti-apoptotic Bcl-2 mRNA rates (Spampanato *et al.*, 2012). Also, another study assessing lovastatin-induced apoptosis in colon cancer cell lines associated with decreased expression of the Bcl-2 and enhanced expression of the Bax rates (Agarwal *et al.*, 1999). To the best of our knowledge, Bcl-2 and Bax expression are generally upregulated in a broad range of human tumor cancerous and are hence can a properate candidate target in many ongoing clinical experiments for GI cancer diagnosis.

Angiogenesis

Obviously the offensive growth of malignant tumor depends on angiogenesis. Angiogenesis is defined as a complex procedure comprising the endothelial cell movement and proliferation, and as well as endothelial cell-mediated degradation of the extracellular matrix (Lee *et al.*, 2014). All polysteps procedure of angiogenesis are essential for cancer improvement and tumor metastasis. Based on the results of (Weis *et al.*, 2008) in human and animal models (in vivo and in vitro studies), statins has a biphasic dose-dependent effect on angiogenesis (angiostatic effects at high therapeutic concentrations and proangiogenic effects at low therapeutic concentrations) which is lipid independent and linked with changes in inhibition of endothelial cell proliferation, induction of apoptosis and vascular endothelial growth factor signaling, and finally reversible by supplementation with geranylgeranyl pyrophosphate and L-mevalonate pathway. Therefore, the seen effects of statins prevention on angiogenesis are primarily related to the absence of L-mevalonate but may not be completely associated for lowering cholesterol (Weis *et al.*, 2008).

Low-dose statins promotes angiogenesis by enhancing endothelial cell proliferation, podokinesis, and migration via activation of endothelial nitric oxide synthase (Kureishi *et al.*, 2000), and are regarded as beneficial for treating cardiovascular diseases (Assmus *et al.*, 2003, Spyridopoulos *et al.*, 2004). Also low-dose statins may improve angiogenesis process, in conformation this procedure of statins treatment several investigation by reducing cholesterol levels and improving endothelial functions (Weis *et al.*, 2008, Jang *et al.*, 2000). Endothelial function and angiogenesis are impaired by hypercholesterolemia.

But during recent years, another outcomes of statins have been appointed which could also be attributed to angiogenesis, in addition to cell-cycle blockade (Park *et al.*, 2001). However, statins does result in signed survival improvements (Kawata *et al.*, 2001), and further, until now it's not reported clinical trials depends on the presence of specific resistance profiles of statins. To the best of our knowledge, this review recommends destruction of overdue increase blood vessels (angiogenesis) by statins therapy (high therapeutic concentrations) and tumors cannot grow outside a critical size or metastasis to another vital organ.

Inhibition of metastasis

Metastasis is known to have lethality effects in cancer patients and involve multiple discrete stages, such as invasion of tumor cells from the primary tumour site, intravasation into the blood or lymphatic circulation and survival in the circulation, extravasation of tumour cells at the target organ site, and the colonisation of tumour cells at the new site (Joyce *et al.*, 2008, Yang *et al.*, 2009, Kenific *et al.*, 2010). (Lee *et al.*, 2014) in an animal model indicated that the growth rate and metastasis of tumours were also significantly prevented when simvastatin was applied to treat CRC. Also, in several transgenic mice models of pancreatic cancer, the intra-peritoneal simvastatin treatment caused to delay in tumor growth and metastasis formation, by the mevalonate pathway prevention (Cao *et al.*, 2014). For discover the exact mechanisms of anticancer activity of statins, cancer researcher must be notice the mitochondria

multiple functions, because of the mitochondrial pathway related to *L*-mevalonate pathway.

Inflammatory and Immunity

Based on a general trend, topical inflammation to be the local immune response, which this immune response could enfold host- tumour-derived, acute-phase proteins, small inflammatory protein mediators (cytokines and chemokines), and allowing immune cells acting in the positional tumour microenvironment, and subsequently thus benefit to patients (Diakos Connie *et al.*, 2014). It must be noticed that the tumor microenvironment, where several types of inflammatory cells in along to tumor cells and extracellular matrix proteins could have interactions with anti-tumor lymphocytes, represents an hostile place where the effector functions of natural killer and T cells are down-regulated indirectly by soluble factors or directly by cell-to-cell contact (Biswas *et al.*, 2006, Korc *et al.*, 2009).

Recently, there is good evidence for interleukin 6 (a pro-inflammatory and multifunctional cytokine) and interleukin 11 roles in the progression of cancer, particularly CRC (Guthrie *et al.*, 2013) and GI cancer (Putoczki *et al.*, 2013), and relationships with necrosis and local and systemic inflammatory responses. Nevertheless, a line with tumour progression, the cytokines alter phenotype and recruitment of the infiltrating immune cells. Also, preclinical studies in animal models and cell lines have reported that the tumor microenvironment seems to have an essential roles in clearing immune cells ultimately possess antitumor or tumour-promoting properties (Diakos Connie *et al.*, 2014).

Basically in all appointed cancers, there is increasing evidence to the fundamental roles that local immune response and systemic inflammation have in recovery of tumors and survival of patients with cancer, and subsequently these inflammatory and immune response against tumor tissue are thought to have play important roles in limiting tumor cell development. Finally the knowledge about inflammatory and immunity responses could to better patient consequences. In addition to, statins are known to have strong immunomodulatory and anti-inflammatory impacts and can have vital roles in the regulation of anti-tumour immunity (Poggi *et al.*, 2010). Therefore, statins family drugs could have been considered to have therapeutics for multiple forms of human disorders such as hypercholesterolemia reduction and cardiovascular risk, gastric cancer, inflammation, autoimmunity and neurodegeneration. Finally, the effects of statins are significantly associated with the reduced cholesterol content of cell membrane, depletion or even the disruption of cholesterol rich membrane micro-domains and/or the inhibition of small proteins such as guanosine triphosphate-binding proteins (Poggi *et al.*, 2010), which ultimately the above reason certainly play a key roles in signal transduction in cancer cells.

Esophageal cancer

Esophageal cancer (EC) is the eighth and fifth most common cause of cancer-related death in women and men, in the all over worldwide (Jemal *et al.*, 2011), and the incidence rates of which has increased particularly in less developing countries. A population-based cohort study in Denmark showed that the use of statins before a diagnosis of EC was related with a 19% reduced in cancer-specific mortality (Nielsen

et al., 2012). The multiple functions of statin drugs (antiproliferative, proapoptotic, antiangiogenic, immunomodulatory, and inhibition metastasis effects) also have been shown in EC cell lines and adenocarcinoma (Ogunwobi *et al.*, 2008, Ye *et al.*, 2012). Statins has a biphasic effect on EC and among clinical trials there were existence considerable heterogeneity about the effects of statins on this cancer (sixth most usual cancer in men). Data from the Q-Research database and the General Practice Research Database, also from a cohort of patients with EC, showed that a higher dose of statins (simvastatin \geq 40 mg or equivalent) may be more beneficial for improvement of EC than low-dose statins (Beales *et al.*, 2012, Bhutta *et al.*, 2012). Based on cohort study of (Alexandre *et al.*, 2016) among subjects who used statins after a diagnosis of EC, the median survival time was 14.9 months compared with 8.1 months for nonusers. Also, in the entire cohort study, the use of statins after diagnosis was related to with a reduced risk of esophageal cancer-specific mortality and all-cause mortality. Occasionally, based on observational studies in all suspected patients with EC during statins therapy an endoscopic surveillance must be administrated prior to definitive genetic testing (especially in child) until surgery is warranted. Basically, decisions are made based on patient's clinical circumstances in addition personal choice.

Gastric cancer

Based on our knowledge, given the well-appointed low toxicity and safety of statins drugs, and in vitro and clinical trials support a proper role for the application of statins in gastric cancer. Overall, statins (lipophilic statins including simvastatin, atorvastatin, lovastatin, fluvastatin, pitavastatin) disrupted and arrested progression of GI cancer, as shown previously in human and animal model (Lee *et al.*, 2014, Poggi *et al.*, 2010, Cao *et al.*, 2011) and a meta-analysis showed a significant reduction in gastric cancer risk with statin use (Chiu *et al.*, 2011, Singh *et al.*, 2013). But various epidemiological studies (Agarwal *et al.*, 1999, Graaf *et al.*, 2004, Haukka *et al.*, 2010) reported that ever-use of any statin (hydrophilic statins including rosuvastatin and pravastatin) did not improve outcome in patients with advanced gastric cancer. In CRC cells, HMG-CoA reductase is quickly overexpressed, HMG-CoA reductase inhibitors decrease senescence and enhance proliferation of endothelial progenitor cells by controlling cell cycle regulatory genes (Assmus *et al.*, 2003), and use of statins therapy could inhibit HMG-CoA reductase activity. The differences between gastric cancer and other tumors cannot be contributed to all tumours responding similarly to statins, and secondly, all statins did not the same effect (Cheng-Qian *et al.*, 2014). Therefore, statins may have chemopreventive activity against cancer and all suspected patients with gastric cancer must be continued to receive routine oncology usual care. Finally, cancer researchers must be noticed that stage of disease and treatment with statins drugs or surgery factors that are associated with an increase in survival rates.

Colorectal cancer

CRC is the third most common malignancy and a common factor of cancer-related mortality globally (Bahrami *et al.*, 2017). The CRC incidence rates in United States (from 2005 through 2014) declined annually by about 2 to 3% (Siegel Rebecca *et al.*, 2018). Decreases in CRC incidence prior to 2000 could be contributed to changes in risk factors and the use of screening, which allows to remove the premalignant lesions

(Edwards *et al.*, 2010). Epidemiologic investigations have shown that use of statins after CRC diagnosis is associated with a reduced risk of cancer mortality (Cardwell *et al.*, 2014), by inhibition of endothelial cell proliferation and induction of apoptosis in CRC cell lines.

(Lee *et al.*, 2014) have indicated that a conventional dose of statins in combination with bevacizumab could decrease the cell viability, migration, invasion, and tube formation of human umbilical vein endothelial cell (HUVEC). The culture media of the CRC cells treated with statins prevent HUVEC invasion by suppressing angiogenic mediators, including angiopoietin 2, binding immunoglobulin protein, and Hsp90 α . Also, the combined treatment with bevacizumab and statins severely decreased the growth and metastases of xenograft tumors in comparison to bevacizumab alone. It is very important to note that researchers after statins therapy attention to signs and symptoms of myotoxicity with the administration of HMG-CoA reductase inhibitors. All suspected patients with GI cancer must be evaluated in endoscopy practices and outpatient gastroenterology for reduction in GI cancer mortality rates.

Statins use and survival rates in clinical trials

The occurrence rate of GI cancer and related disorder has been promoted in most regions of the worldwide. The gastric cancer is one of the three leading main cancers that causes death (0.7 million, 8.8%) particularly in less developing countries due to a lack of early detection and access to treatment of facilities (50), and naturally these proportions will be rising further by 2025. In recent years, studies conducted in humans on the effect of statins on survival for some types of tumours (liver cancer, acute myeloid leukaemia and non-serous-papillary epithelial ovarian cancer) have indicated increased survival in advanced (Graf *et al.*, 2008, Habis *et al.*, 2014). In the Scandinavian Simvastatin Survival Study trial (Pedersen *et al.*, 2000) and a nested case-control study from the Netherlands (Graaf *et al.*, 2004) showed a significant reduction in the incidence of all cancers and fewer cancer-related deaths among statin users as compared with nonusers, which increased with increasing duration of use.

Statins and cancer risk and prevention

It has been reported that patients with advanced cancer cannot usually understand intent of their cancer treatment and rarely engage in discussions about their preferences for care at the end of life (Weeks *et al.*, 2012). The incidence estimates for 2012 show that there were 32.6 million people (over the age of 15 years) alive who have had a cancer diagnosed in the previous five years (50), for example the percentage diagnosis rate in colorectum cancer was equal to be 9.7% (1.4 million) in 2012.

The early detection and diagnosis of a suspected patients with GI cancer has principal implications for management and improvement of the patients. In suspected patients with GI cancer practical testing must be done by immunohistochemical testing methods, screening for CRC test by colonoscopy or flexible sigmoidoscopy, endoscopy, magnetic resonance imaging and/or endoscopic ultrasound, and gene mutation analysis for diagnoses type of cancer in first- and second-degree relatives to control measures and GI cancer prevention globally. In addition, more recent rapid decreases (CRC incidence rates) are assumed to primarily reflect enhanced intake of

colonoscopy, which now is the predominant screening test (Cress *et al.*, 2006, Siegel *et al.*, 2012, Olfati *et al.*, 2018, Emami *et al.*, 2017, Bayati Zadeh *et al.*, 2015). Also, in suspected person must be done to at risk for familial GI cancer if they (i) have a known as genetic syndrome associated with GI tract. And to better consider the role of prognostic risk repair of statins drugs medications, additional observational studies applied involving chemotherapy, surgical and radiotherapy patients could be useful to diagnose whether a true additive therapeutic benefit to above therapeutic methods are apparent. Finally, the monitoring the process of GI cancer incidence could facilitate efforts for cancer treatment, control, and prevention. Also, after statins treatment (about low- and middle- risk patients), additional follow-up of these patients must be necessary to affirm a potential profit of statin use.

Concluding remarks

Based on our knowledge in this review, after statins therapy for improvement of GI cancer, hypercholesterolemia reduction and cardiovascular risk diagnosis could also be recognized, because these factors into both cancer screening and genetic risk assessment guidelines recommendations. Thus, the routine review of lipid and cardiovascular records could be helpful in specific cases where the GI cancer site is in question. If cancer researchers monitor the systemic statins treatment response, we can get useful feedback of GI cancer activity after therapeutic interventions. In conclusion, the authors of this review suggest that long-term and high therapeutic concentrations statins use have chemopreventive effects.

Future perspectives

The focuses of future clinical trial on this chronic toxicity round about the side effects of HMG-CoA reductase inhibitors should be on cell and plasma membrane function, small inflammatory protein mediators, calcium regulation, and drug interactions. Further experiments are needed to convers the underpinnings of sickness understanding in these patient, and how best to assistance them in their future care. Also future investigation must be concentrate the indicators (such as C-reactive protein) to have a role in the early diagnosis and to monitor GI cancers and autophagy system that induce by statins.

Declaration of conflict of interests

None

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