Potential Anti-Tumor Activity of Intravenous and Subcutaneous Immunoglobulin

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Polyvalent human immunoglobulin (Ig) is one of the most intriguing and powerful therapeutic strategies available. It was originally used as replacement therapy in antibody deficiencies. The discovery of the immunomodulatory effects of high doses of intravenous immunoglobulins (IVIG) has led to their use as treatment for several inflammatory and autoimmune diseases. In the last few years, even immunoglobulins administered subcutaneously (SCIg) have been successfully used in selected immune mediated diseases [1]. Several mechanisms of action have been suggested to explain the mode of action of IVIG-mediated immunomodulation and they vary according to the nature of the disease, whereas the precise mechanism of action of SCIg is not completely understood.

Besides this role in immunomodulation, other studies involving cancer cell lines and animal models described the anti-tumorigenic effect of IVIG [2-4]. There are no reports on the role of SCIg.

PATIENT DESCRIPTION

We describe the case of a 60 year old man with pancreatic cancer who was treated with SCIg for common variable immunodeficiency (CVID). His medical history showed splenectomy for idiopathic thrombocytopenic purpura. The diagnosis of CVID was made 10 years before cancer development due to the presence of recurrent upper respiratory tract infections and confirmed by specific lab analysis (IgG 246 mg/dl, IgA 6.67 mg/dl, IgM 27 mg/dl with impaired response to a booster of tetanus vaccination).

Our patient benefited from IVIG treatment (300 mg/kg every 4 weeks for 2 years). However, he stopped treatment after major cardiovascular events that required percutaneous coronary intervention.

In 2012, during a routine checkup, the patient described a recent onset of fatigue and lack of appetite. A computed tomography (CT) scan showed a large lesion involving the isthmus of the pancreas, with regional lymph node involvement and hepatic metastases. The patient began chemotherapy with irinotecan, 5-fluor uracil and folinic acid (FOLFIRI). Despite the poor survival prognosis, we decided to restart Ig replacement therapy. He started weekly 20% SCIg therapy (Hizentra® [CSL Behring King of Prussia, PA, USA], 400 mg/kg monthly) to avoid cardiovascular complications. Before the immunoglobulin treatment began, the patient's life expectancy was only a few months. Surprisingly, after 1 month of SCIg therapy, the patient started to feel better, with a slight improvement in results from laboratory analysis. This improvement lasted for 10 months. The patient died due to metastases leading to massive pulmonary and hepatic impairment.

COMMENT

With regard to the efficacy of IVIG for cancer treatment, few published studies are available and they mostly describe patients with neoplastic disease who are receiving Ig treatment for concomitant autoimmune diseases or immunodeficiency. One of the first reports referred to a patient presenting with human immunodeficiency virus and polymyositis who developed Kaposi's sarcoma after immunosuppressive treatment and recovered due to IVIG therapy (2 g/kg monthly).

In 2001, IVIG monotherapy (2 g/kg monthly for 8 months) for a patient being treated for melanoma led to a significant regression of the metastases in the liver and stabilization in the lung (all tumors < 1 cm). Unfortunately, when the patient later developed bone and subcutaneous metastases, the combined treatment with IVIG, interferon, and chemotherapy did not prevent a poor outcome 14 months after the start of IVIG treatment.

In an open label trial, two patients with metastatic melanoma receiving IVIG (1 g/kg every 3 weeks for 6 courses after chemotherapy failure) showed a disease stabilization that lasted for 3 and 8 months, respectively.

Treatment with IVIG (0.4 g/kg per month) led to a prolonged disease free period (30 months vs. 3 months) in a patient with malignant peripheral nerve sheet tumor and multiple sclerosis, after unresponsiveness to chemotherapy, radiotherapy, and surgery.

A complete remission of thymic carcinoma that was unresponsive to chemotherapy and bone marrow transplantation was achieved in a patient receiving IVIG (2 g/kg) for a concurrent myasthenic crisis.

We also reported Ig treatment efficacy in 91 patients with polymyositis and dermatomyositis [5]. After a 28 year follow-up period, patients treated with corticosteroids

and immunosuppressants had higher rate of mortality compared to those receiving IVIG and/or SCIg (29.2% vs. 14.5%, respectively). Gender and other prognostic factors did not seem to influence the results. This finding might reflect the benefit of Ig treatment in cancer-prone patients who also present with autoimmune diseases.

The immunomodulatory role of Ig derives from its key role in the adaptive immunity and in the maintenance of immune homeostasis, which are both altered in autoimmune diseases and cancer [2-4]. However, in these two conditions Ig efficacy is due to two opposite mechanisms. While in autoimmune diseases Ig action is derived from its anti-inflammatory activity (classical: macrophage colony stimulating factor mediated), in neoplasms, Ig acts in a pro-inflammatory direction (alternative: granulocyte-macrophage colony-stimulating factor mediated) [4]. These different modalities of Ig activity depend on macrophage polarization, as the result of a macrophage switch from classical to alternative polarization, in response to the Ig stimulus. IVIG exerts its anti-tumorigenic effect by means of a synergic cooperation of several mechanisms, Fc, and F(ab) mediation, which act both on tumor growth and metastasis spread [2-4] [Table 1].

Today, cancer is the major cause of death in patients with CVID. It would be interesting to investigate whether in those CVID patients who have not been treated with Ig (IVIG or SCIg) due to intolerance, long diagnostic delay, or drug availability are later more prone to develop a neoplasia. If so, the problem could be that not giving Ig to a CVID patient means a higher risk of developing neoplasia.

Table 1. Discussed IVIG mechanisms of action in cancer

Activation of FCGR	Stimulation of NK cells cytotoxic activity on tumor cells
Effects on cells proliferation	Increased expression of pro-apoptotic molecules (p53, p21, Fas) and arrest of the cell cycle at the C1 phase
Effects on cytokine and chemokine production	Increased expression of IL-12 and IL-10 and reduced expression of the *CCL2* gene
Effects on metastasis spread	Anti-VEGF Ab and reduced expression of metalloproteinases and anti-RGD Ab Induction of interleukin-12 secretion, leading to NK-cell activation Suppression of tumor cell growth Hindrance of nuclear factor κB activation and IκB degradation Increased production of pro-apoptotic molecules and Fas expression G1 cell-cycle arrest
Natural antibodies	Recognize oligosaccharides expressed by tumor cells with cytotoxic or bystander effect

anti-RGD Ab = anti-vascular endothelial growth factor therapy, adhesion molecule, anti-VEGF Ab = anti-vascular endothelial growth factor therapy, angiogenetic effect, FCGR = Fc gamma receptors, IL = interleukin, IVIG = intravenous immunoglobulins, NK = natural killer cells

CONCLUSIONS

This case study and brief review shows that IVIG can have an inhibitory role on growth and tumor spread in both solid neoplasms and lymphoproliferative diseases. Various molecular and cellular pathways are involved in this fight against tumor growth and spread, although the specific manifestations are not completely understood. There are no available data on SCIg and cancer. It is thus possible that the administration of IVIG supplemented with SCIg can help in the treatment of cancer itself and its metastases. More experimental and clinical data are necessary to confirm these preliminary observations.

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Capsule

An IgG1 SNP enhances autoimmunity

One common feature of autoimmune diseases like systemic lupus erythematosus (SLE) is the presence of high titers of self-reactive antibodies. These antibodies result in immune complexes, inflammation, and tissue pathology. Consequently, the checkpoints that normally keep immunoglobulin G (IgG)-positive autoreactive B cells in check are of intense interest. **Chen** et al. reported the presence of a common IgG1 single-nucleotide polymorphism (SNP) in East Asian populations (hIgG1-G396R). This SNP was enriched in SLE patients and associated with increased disease severity. Humans with this SNP, as well as knockin mice, showed enhanced plasma cell accumulation and antibody production. This SNP enhanced IgG1 immunoglobulin tail tyrosine motif phosphorylation, triggering longer adaptor protein Grb2 dwell times in immunological synapses and hyper–Grb2–Bruton's tyrosine kinase signaling after antigen binding.

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