دور العــلاج المناعــي فـــى الأورام الخبيثــة للمسالك البوليــة

رسالة
توطئة للحصول على درجة الماجستير
فى المسالك البولية

مقدمة من
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المقدمة

العلاج المناعي هو وسيلة جديدة من العلاج تستخدم الجهاز المناعي للمريض إما عن طريق الاستشارة المباشرة للدفاعات الطبيعية لهذا الجهاز أو عن طريق مكونات الجهاز المناعي المستخلصة أو المصنعة ضد الأمراض.

يعتبر العلاج المناعي الآن الطريقة الرابعة فى علاج الأورام السرطانية إما باستخدامه وحيدا أو كعامل مساعد للجراحة و العلاج الكيماوي و الإشعاع.

أثبت الـ (بى _سى _جى) أنه أكثر أنواع العلاج المناعي فاعلية حتى وقتنا هذا فقد أوضح أن الـ(بى_سى_جى) عند حقنه فى مثانة مرضى أورام سرطان الخلايا الانتقالية السطحي يتسبب فى وجود عدة أنواع من سيتوكينات فى بول المرضى، من هذه السيتوكينات (انترفيرن جاما _ انترلوكين_12) الذى اثبت أن لهم تأثير مضاد على تكوين أوعية دموية جديدة. هذا يفترض انه بالإضافة إلى دوره فى رد الفعل المناعي الخلوي فأن الـ (بى_سى_جى) قد يكون له دور فى خلق بيئة مضادة لتكوين أوعية دموية جديدة الذى يساعد على منع نمو الورم وتوغله فى المستقبل.

وقد أجريت بعض التجارب العشوائية لعلاج 160مريض باستخدام مزيج من انترفيرون الفا و فينلاستين وحيدا فى علاج سرطان الكلية الخلوي، وقد لوحظ التحسن فى معدل الاستجابة بالإضافة إلي مستوى النجاة فى الذين عولجوا باستخدام انترفيرون حيث كانت معدلات التحسن 16.5%، 2.5% على الترتيب ومتوسط النجاة 15.8 ، 8.8 شهور مقترحة ان الانترفيرون كعامل وحيد قد يزيد النجاة حيث أن النشاط الاكلينيكي للفنبلاسين ضئيل.

يحتوى لقاح فى مكوناته على الانتيجين الخاص بالبروستاتا و الذى يساعد مرضى سرطان البروستاتا فى مراحله المتقدمة. باحثون فى مركز دانا فاربا فى بوسطن عالجوا ثلاثة و ثلاثين مريض أجريت لهم جراحة لاستئصال البروستاتا لوحظ فيهم ارتفاع معدلات هرمون ال بى آس آيه علاجهم باستخدام مصل يحتوي فى مكوناته على بى آس آيه، أربعة عشر مريض من الثلاثة والثلاثون كانت حالتهم مستقرة علي الأقل ستة أشهر بعد أول تطعيم، تسعة مرضى كانت حالتهم مستقرة لمدة 11–25 شهر، وستة من هؤلاء استقر مستوى بى اس ايه ولم يتطور المرض طوال فترة الدراسة.

Role of Immunotherapy In Urological Malignancies

Essay
Submitted for partial fulfillment
Of master degree of urology

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Introduction

Immunotherapy is a new mode of treatment that uses the patient's immune system either through direct stimulation of this system's natural defenses or by using synthetic or extracted immune system components against disease **(Salgaller; 2000).**

Immunotherapy is now considered the fourth modality in treating cancer, either acting as a monotherapy, or as an adjuvant to surgery, chemotherapy and radiation.

Regarding Urological malignancies, the most proven and effective form of immunotherapy till now is the use of Bacillus Calmette-Guerin (BCG) in managing superficial bladder transitional cell carcinoma (TCC). It has been shown that BCG induces a variety of cytokines in the urine of patients with superficial TCC, during intravesical BCG immunotherapy of bladder TCC; these cytokines include interferon-gamma (IFN-gamma), and interleukin-12 (IL-12) that have an atiangiogenic action. This suggests that in addition to a cellular immune response, BCG may induce a cytokine mediated atiangiogenic environment that aids in inhibiting future tumor recurrence and progression **(Poppas; 1998).**

Several randomized trials have recently compared therapeutic approaches using interferon-alpha (IFN-a) in the treatment of metastatic renal cell carcinoma. One trial reported treating 160 patients with either a combination of IFN-a and vinblastine or vinblastine alone in the treatment of renal cell

carcinoma (RCC); the response rates were 16.5% and 2.5% respectively, and the median survivals 15.8 and 8.8 months suggesting that interferon as a single agent may enhance survival since the clinical activity of vinblastine is minimal **(PyrhOnen et at., 1999).**

Prostatic- specific antigen (PSA) -based vaccine may help men with advanced prostate cancer. Researchers from Dana-Farber Cancer Institute in Boston gave three consecutive monthly doses of a recombinant vaccinia virus encoding PSA to 33 men with rising PSA levels after radical prostatectomy, radiation therapy or both. Some of the patients had cancer that had already spread beyond the prostate. 14 of the 33 men were staHle for at least 6 months after the first immunization, nine patients remained stable for 11 to 25 months and six of those had stable PSA levels and no reported disease progression during the study **(T.J. Koerner, American cancer society (ACS), 2004).**

Aim of the work

To demonstrate the basic principles of tumor immunology and the contemporary role of immunotherapy in bladder cancer, renal cell carcinoma and prostate cancer, areas for further exploration, and potential applications.

Protocol of Essay

References:

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BASIC IMMUNOLOGY

Immunity is defined as resistance to disease; basic immune responses can be divided into:

A: innate (non adaptive)

B: specific (adaptive) effector mechanisms

A: INNATE IMMUNITY

The innate immune system does not possess antigen specificity, and cannot adapt to recognize an organism which has evolved to evade it. It consists of:

- Physical barriers: such as mucosal epithelium
- Phagocytic cells: Monocytes, macrophages and neutrophils
- Soluble mediators: C-reactive protein (CRP), mannose binding lectin (MBL), cytokines
- Soluble enzymatic cascades as the complement system, which is activated directly by exposure to pathogens and serves to directly lyse the pathogen, or to enhance and target the activity of innate and specific effector cells by opsonisation and activation via cell surface receptors for complement components.

Complement

The complement system, is a soluble enzymatic cascade which focuses and amplifies the activity of the specific and

innate immune systems as well as having lytic activity against bacteria, it is a part of the innate immunity as it has no antigen specificity.

Complement cascade can be activated either through a classical pathway involving an antigen antibody immune complex which binds circulating complement C1q to the Fc region of the antibody tail, or can be activated through an alternative pathway, triggered by contact with exposed bacterial capsules without the need for prior antibody production.

B: SPECIFIC IMMUNE RESPONSE

Specific (adaptive) immune responses are more effective than innate ones, it consists of:

- Cellular (cell mediated) immunity: T lymphocytes (CD4+ = 'Helper'), (CD8+ ='Cytotoxic'), and B lymphocytes
- Humoral: antibodies and cytokines (Kaufman et al., 2000)

T and B lymphocytes possess infinitely variable antigen receptors which can clonally expand. Antibodies can activate complement and enhance opsonisation of antigen via phagocyte surface receptors for the Fc region of immunoglobulins (FcR). Both innate and adaptive mechanisms exponentially amplify the immune response, since clonal expansion of lymphocytes increases the number of cells reactive with an antigen. Cytokines and complement components recruit other immune

effector mechanisms and antibodies activate complement and phagocytes.

T helper cell responses which help antibody production by B cells are called Th2 type responses, and those which promote the inflammatory activity of phagocytes such as macrophages are called Th1 type **(Raftery et al., 2000).**

I- Antigens

An antigen is any substance which can elicit a specific immune response. An antigen consists of many epitopes. An epitope is a specific sequence of a protein or carbohydrate recognized by the receptor molecule of the immune system (antibody or T cell receptor), although an antigen usually elicits an immune response, if the antigen is encountered in appropriate circumstances the immune system response may be switched off **(Egner et al., 2000).**

II- Antibody

An antibody is a soluble protein immune receptor that is produced by B lymphocytes, and consists of two identical antigen-binding sites. The antigen specificity of the antibody resides in the antigen-binding variable regions (the fragment antigen-binding, Fab, portion) **(Egner et al., 2000).**

Most antibody immune responses are polyclonal (many cell clones expand, each recognizing different, sometimes overlapping, epitopes on the antigen); oligoclonal responses occur when a limited number of clones expand for some reason