nomas did not demonstrate any positive immunoreactivity which corroborates other studies of primary malignant melanomas [6, 12].

Only one glioma displayed detectable c-*erb*B-2/HER2 immunoreactivity, and this uncommon expression of c-*erb*B-2/HER2 protooncogene in human glioma tissues is in agreement with some [6,7] but not with other reports [3,5]. These discrepancies may be related to different methods, tissue processing and/or antibodies used. The low levels of c-*erb*B-2/HER-2 protein in the examined gliomas are in contrast to their abundant epidermal growth factor receptor expression shown earlier [13].

In conclusion, we have shown that immunohistological cellular staining for c-*erb*-B2/HER-2 protein was limited to neoplastic intracranial tissues, principally meningiomas and metastatic carcinomas.

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Feature Articles

The Use of Immunotoxins for Cancer Therapy

Lee H. Pai and Ira Pastan

INTRODUCTION

IMMUNOTOXINS ARE a new class of cytotoxic agents composed of bacterial or plant toxins coupled to monoclonal antibodies or growth factors [1, 2]. Toxins are highly active protein molecules that enzymatically inactivate protein synthesis, leading to cell death. When coupled to a ligand (monoclonal antibody or growth factor), the resulting molecule can specifically target and kill cells that present the specific antigen or growth factor receptor on their surface.

The progress made in fields of immunology and molecular biology have let scientists select more specific and potent ligands and toxins for target therapy. In this article, we will discuss the structure and function of commonly used toxins, the clinical activity of the first generation immunotoxins and their problems, the production of recombinant toxins and prospects for the future.

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TOXINS

Several bacterial and plant proteins have been used to prepare immunotoxins. Of these, ricin, Pseudomonas exotoxin A (PE), and diphtheria toxin (DT) are the most extensively investigated. The bacterial toxins, Pseudomonas exotoxin A (PE) and diphtheria toxin (DT), ADP-ribosylate and thereby inactivate elongation factor 2, an enzyme necessary for protein synthesis. PE, a 66 kD protein secreted by *Pseudomonas aeruginosa*, is composed of three major structural domains [3, 4]: an amino-terminal cell-binding domain (domain I), a central translocation domain (domain II), and a carboxyl-terminal activity domain (domain III). Domain III catalyses the ADP ribosylation and inactivation of elongation factor 2, which inhibits protein synthesis and leads

to cell death. DT is a 58 kD protein produced by *Corynebacterium diphtheriae*. Like PE, DT is also composed of three domains; the catalytic domain, termed fragment A, is responsible for the ADP ribosylation activity. Fragment B consists of two domains, a receptor-binding domain and a transmembrane domain which is responsible for membrane insertion and translocation [5].

The plant toxins generally inactivate ribosomes by cleaving a specific sequence in 60S rRNA. Ricin is a 65 kD glycoprotein purified from the seeds of the castor bean (*Ricinus communis*). It is composed of an A chain, which kills the cell by catalytically inactivating its ribosomes, linked by a disulphide bond to a B chain, responsible for cell binding, and contributing to translocation of the toxin across the cell membrane. Immunotoxins made of whole ricin lack specificity, because the B chain binds to galactosyl residues of glycoproteins and glycolipids present on the surface of many cells. To decrease the non-specific binding of whole ricin, the A chain alone, obtained by cleavage of the disulphide bond linking it to the B chain or by expression in *Escherichia coli*, has been used for coupling to antibodies. The resulting immunotoxins have higher specificity but are less active than immunotoxins made with whole ricin. Another approach to decreasing the non-specific binding of ricin is to react whole ricin with a glycopeptide that blocks the galactose binding sites or to deglycosylate the A chain [6].

IMMUNOTOXIN CLINICAL TRIALS

Recent clinical trials using immunotoxins produced by chemical coupling have shown some encouraging results. Vitetta and colleagues have reported two phase I trials of immunotoxins consisting of a monoclonal antibody binding to CD22 that is coupled to deglycosylated ricin A chain [7, 8]. The antibody (RFB4) recognises an epitope that is present on normal pre-B and resting B cells, as well as on a spectrum of B cell neoplasms [9]. 25 patients received whole IgG-dg A and 15 patients received Fab'-dg A. All these patients had non-Hodgkin lymphoma (NHL). Immunotoxins were delivered by intravenous (i.v.) intermittent infusions over 8 days. The maximum tolerated dose (MTD) was 75 mg/m^2 for the Fab' and 24 mg/m^2 for whole IgG. Dose-limiting toxicities included pulmonary oedema, aphasia and rhabdomyolysis. Other side-effects include hypoalbuminemia, fluid retention, myalgia and low grade fever. Complete and partial responses were observed in 45% of the patients who received doses > 50% of the MTD. However, the majority of the responses were transient, lasting 1–4 months. Of the patients that received IgG-dg A, 20–24% developed human anti-ricin antibodies (HARA) and human anti-mouse antibodies (HAMA). However, only 7% of the patients treated with Fab'-dg A developed HAMA; 24% of the patients developed HARA in this group. A phase I trial using continuous infusion of IgG anti-CD22-dg A is presently being carried out.

Grossbard *et al.* reported a phase I trial using anti-B4 blocked ricin administered by daily bolus injections to patients [10]. B4 recognises the CD19 antigen which is present on normal and malignant B lymphocytes. A total of 25 patients were treated; 23 had non-Hodgkin lymphoma, 1 had non-T acute lymphoblastic leukaemia (ALL) and 1 patient had chronic lymphoblastic leukaemia (CLL). Toxicity included transient elevation of hepatic transaminases, transient thrombocytopenia, fever and hypoalbuminemia. The MTD was 250 μg/kg. One complete response and two partial responses were reported. 8 patients had transient reductions of adenopathy lasting less than 4 weeks. HAMA and HARA were observed in 13 patients. A second phase I trial was carried out using a 7-day continuous infusion [11]. A total of 43 patients were treated; 33 had NHL, 5 had CLL and 5 had non-T ALL. Toxicities were similar to that observed in the previous study with elevations of serum glutamic-oxalacetic transciminase (SGOT) and serum glutamic-pyruvic transciminase (SGPT) being dose limiting. Two complete responses, five partial responses and 12 transient responses were reported. 26 patients developed HAMA or HARA which limited retreatment. A third trial using anti-B4-BR for NHL patients postautologous bone marrow transplant is presently ongoing at the CALGB institutions.

While these immunotoxin trials showed encouraging results for treating haematological malignancies, therapy of solid tumours with immunotoxins has been less successful and has encountered some difficulties [12–15]. PE chemically coupled with OVB3, a murine monoclonal antibody (mAb) that reacts with human ovarian cancers, was administered intraperitoneally to 23 patients with minimal residual disease [14]. Dose-limiting toxicity was due to lethal central neurological toxicity, observed at 10 μg/kg. Other toxicities included transient liver enzyme elevation, low-grade fever, nausea and abdominal pain. The neurotoxicity was due to reactivity of OVB3 with certain areas of normal brain; this reactivity was not detected during preclinical screening. In another phase I trial using Mab 260F9 coupled to recombinant ricin A chain (15), severe sensorimotor neuropathy occurred in 3 out of 5 patients. 260F9 is a murine antibody that recognises an antigen present on the surface of breast cancer cells. Subsequently, reactivity of 260F9 with Schwann cells was detected by immunoperoxidase staining.

SECOND GENERATION IMMUNOTOXINS FOR SOLID TUMOURS

Experience acquired from these trials indicated that these immunotoxins effectively kill cells expressing a specific antigen on their surface. Because of this specificity, antibodies selected for use as immunotoxins should react with antigens present only on tumour cells. Unfortunately, in selecting monoclonal antibodies to target solid tumours, this level of specificity may not be possible to achieve, so it is advisable that any cross-reactivity should be restricted to non-essential tissues. In addition, the antibody should also react with similar non-essential tissues of non-human primates (or other animals used for preclinical toxicity studies) to permit a thorough preclinical evaluation of toxicity.

Major progress has also been made in minimising the non-specific toxicity of the toxins. The identification of genes encoding PE, DT and proricin has allowed scientists to clone and express these toxins in *E. coli*. Genetically modified toxins with more desirable biological properties can be easily designed and produced [2]. For example, deletion of domain Ia of PE produces a 40 kD protein that is much better tolerated by animals than the native PE, because it cannot bind to cellular receptors. PE40 and other recombinant forms of PE have been used to make second generation immunotoxins that have a much larger therapeutic window in mice bearing human xenografts.

A second generation immunotoxin for solid tumours, termed LMB-1, has been recently developed [16]. LMB-1 is an immunotoxin in which murine MAb-B3 is chemically linked to PE38, a recombinant form of Pseudomonas exotoxin, that lacks the cell-binding domain and some other non-essential sequences. MAb-B3 (IgG1κ) has strong reactivity with many human solid tumours including colon, gastric, oesophageal, lung, bladder and breast carcinomas [17]. MAb-B3 has limited reactivity with normal human tissues but does react with glands of the stomach and the

epithelium of the oesophagus, trachea and bladder. Similar reactivity is present in monkey tissues. LMB-1 has excellent activity agaisnt cultured cancer cells and causes complete regression in immunodeficient "nude" mice bearing human tumour xenografts that express the B3 antigen. When given to Cynomolgus monkeys, limiting toxicity occurred at five times the dose needed to cure xenografts in mice and consisted of gastric mucosa necrosis and haemorrhage. This toxic effect is related to B3 expression which was predicted by the immunohistochemical studies. A phase I clinical trial using LMB-1 in patients with solid tumours is being conducted at the National Cancer Institute.

C242-NLysPE38 is another PE immunotoxin that is presently undergoing preclinical evaluation [18]. C242 is a Mab that recognises a sialylated carbohydrate epitope present on many human colon, pancreas and cervical cancers. When coupled to PE38, the resulting immunotoxin has been shown to have excellent anti-tumour activity.

RECOMBINANT TOXINS

Because the microvasculature of human solid tumours is abnormal, macromolecules such as immunotoxins (molecular weight ~ 200 kD) might be poorly distributed into bulky tumours, hampering their efficacy. The production of genetically engineered single-chain immunotoxins which are smaller in molecular size (molecular weight ~ 66 kD) may overcome this problem [19]. These second-generation immunotoxins are composed of the variable regions of the light and heavy chains of antibodies directly fused to the toxin. Several single-chain immunotoxins have been cloned and produced to date. Preclinical testing of these recombinant toxins has shown that they retain full *in vitro* cytotoxicity and have superior antitumour activity in laboratory animals. Because of their small size, single-chain immunotoxins should penetrate and distribute more readily in large tumours than the chemical conjugates presently being used. LMB-7, a single-chain immunotoxin composed of the variable (Fv) regions of MAb-B3 fused to PE38 [20] is presently undergoing preclinical testing in monkeys. It should be available for clinical testing in cancer patients within a year.

Chimeric toxins have also been made by fusing a portion of a toxin gene to cDNA encoding growth factors and cytokines. These include transforming growth factor (TGF)α, insulin-like growth factor (IGF)1, acidic and basic fibroblast growth factor (FGF), interleukin (IL)2, IL4 and IL6 [2]. These recombinant toxins target tumour cells that express specific receptors on their surface.

DAB486IL2, a recombinant fusion protein in which the receptor-binding domain of DT has been replaced with human IL2 [21] is presently being tested in patients with IL-2 expressing tumours. Over 100 patients with malignancies that express IL2 receptor have been treated on different dosage schedules. Toxic effects include transient elevation of transaminases, fever, hypoalbuminemia and reversible changes in serum creatinine. In one of these studies [22], 6 out of 18 patients treated with daily i.v. bolus of DAB486IL2 for 10 doses had anti-tumour effects, 3 patients entered remissions lasting from 5 to 30+ months. Fifty per cent of the patients developed antibody against DT in this study. Because most of the patients might have had prior immunisation against DT, the presence of preformed neutralising antibodies might reduce the activity of the DT immunotoxins.

A phase I trial using TP40, a recombinant fusion toxin in which TGFα is fused to a mutant form of PE lacking the cell-binding domain [23], has recently been completed in patients with superficial bladder cancer. A total of 43 patients were treated with escalating doses of TP40. Treatment was given weekly for 6 weeks by intravesical administration (0.15–9.6 mg/week). No systemic or local toxicity was observed in this study. 11 patients had evaluable Ta or T1 lesions, 19 had resected Ta or T1 lesions, 7 had carcinoma *in situ* and 6 patients had mixed CIS and Ta/T1 disease. Eighteen tumour samples were tested and all were positive for epidermal growth factor receptors. At the doses and regimen used, TP40 was not active against Ta of T1 lesions and did not appear to prevent recurrence of Ta or T1 lesions. However, evidence of activity was observed in the group of patients with CIS. 6 out of 13 patients had cystoscopic improvement; 2 patients had negative biopsies and 1 has remained in remission for more than 5 months. None of the patients developed antibodies against TP40.

PROSPECTS AND PROBLEMS

An additional clinical problem that needs to be overcome is the production of antibodies against immunotoxins; neutralising antibodies can usually be detected within 10 days of the first administration. This limits therapeutic efficacy by precluding further treatment. Concomitant use of immunosuppressive agents such as cyclosporine, cyclophosphamide or 15-deoxyspergualin [24] might help suppress human antibody production to both the mouse antibody and toxin. An alternative strategy is to chemically modify the toxin so that it is less immunogenic by chemically coupling it to polyethylene glycol [25], as has been done for adenosine deaminase.

Although immunotoxins are still in the early stages of clinical development, the objective responses observed in recent studies are very encouraging. During the next decade, new generations of recombinant immunotoxins with higher specificity and potency should be available. The selection and treatment of cancer patients with a small tumour burden and concomitant therapy with radiation and/or cytotoxic drugs might improve the prognosis for many who have diseases for which there is currently no cure.

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Cancer Incidence in the Commonwealth of Independent States, the Baltic States and Georgia—The Former U.S.S.R.

David G. Zaridze and Tamara Basieva

INTRODUCTION

LITTLE DETAILED information has been available about cancer patterns in the former Union of Soviet Socialist Republics (U.S.S.R.) for a variety of reasons [1, 2]. However, there has been an attempt to present broad cancer patterns in republics which comprised this territory [3]. This publication covered the period between 1969 and 1971 and included only nine diagnostic categories in men and 11 in women by six age groups, reflecting the layout of the data collection form for cancer incidence statistics used in the U.S.S.R. until 1989. The list of cancer sites was far from being complete and excluded, for example, cancer of the colon, liver, pancreas, corpus uteri, prostate, while the category of skin cancer included both malignant melanoma and other skin neoplasms. Recently, mortality data and the corresponding population information have become available [4]. Changes in the former U.S.S.R. from the mid-1980s have resulted in the increased availability of cancer incidence and population information.

The territory of the former U.S.S.R. is vast and the differences in lifestyles and environmental exposures between the republics are also large. Accordingly, it is of great interest to know the underlying cancer patterns and how these relate to the different exposure patterns.

Cancer diagnosis and treatment services in the former U.S.S.R. have been centralised and this has enabled a central register to be maintained in the republics regarding all cases of cancer diagnosed and treated in these territories. Registration of all patients with newly diagnosed cancer, including cancers diagnosed at the time of death or at autopsy in the former U.S.S.R. was the responsibility of oncological dispenseries (hospitals) which served defined catchment areas. They collected information about cancer patients and presented annual statistical reports at the level of the oblast and republic.

Cancer registration in the former U.S.S.R. had many shortcomings including non-systematic and low-level control over data quality [1]. The use of indices of reliability provides some insight into data quality, suggesting that there are some regional differences in quality of diagnosis and registration. For example, the proportion of morphologically (histologically or

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