TUMOUR TARGETING

Efficient delivery

One way to reduce the side effects of cancer chemotherapy on healthy tissues is to design targeted drugs; another is to use special delivery systems to deliver a drug specifically to the cancer cells. Tamara Minko and colleagues now report a system that delivers camptothecin selectively and effectively to ovarian cancer cells in a mouse model.

The authors constructed a targeted drug delivery system comprising polyethylene glycol (PEG) as a carrier, the anticancer agent camptothecin (CPT), and a modified luteinizing hormone-releasing hormone (LHRH) peptide as a targeting moiety. LHRH is overexpressed in ovarian cancer cells and LHRH receptors are only expressed at low levels in healthy ovarian tissue.

When mice bearing human ovarian cancer xenografts were treated with CPT alone, tumours were reduced in size, non-targeted CPT–PEG had increased activity and CPT–PEG–LHRH resulted in the greatest reduction of tumour size. Tumour-cell killing was shown to be by apoptosis, probably due to the increased concentration of CPT entering the cancer cells. To confirm the targeting of the LHRH-conjugate to the ovarian tumours, the authors looked at the distribution of tritium-labelled polymers in the treated mice. Both PEG alone and LHRH–PEG accumulated preferentially in tumour tissue — this is in line with a form of passive targeting known to occur in tumours called the enhanced permeability and retention effect. The level of accumulation of LHRH–PEG was nearly twice that of PEG alone, confirming the active tumour-targeting capacity of this polymer.

As LHRH is secreted in the pituitary gland and stimulates the production of hormones that are essential for the regulation of normal reproductive function it is vital that the drug conjugates do not cross the blood–brain barrier or affect reproductive function. In mice with or without tumours, the conjugates did not cross the blood–brain barrier and no cell death was seen in brain tissues. Furthermore, the secretion of LH by the pituitary cells was not reduced in treated mice, and all female mice were able to produce healthy viable offspring whether or not they were treated with CPT–PEG–LHRH.

So, this drug delivery system is effective at targeting ovarian cancer in mice, with reduced side-effects. As LHRH is also overexpressed in breast and prostate cancer, this system should be explored for the treatment of these cancers too.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Dharap. S. S. *et al*. Tumor-specific targeting of an anticancer drug delivery system by LHRH peptide. *Proc. Natl Acad. Sci. USA* **102**, 12962–12967 (2005)

TRIAL WATCH

Immuno attack

Cel-Sci Corporation have approval from the Canadian regulatory agency for biological agents to initiate a phase III trial of their immunotherapeutic agent, Multikine, in patients with advanced primary squamous cell carcinoma of the oral cavity.

Multikine is a mixture of naturally occurring cytokines, including interleukin-2, other interleukins, interferons and colony-stimulating factors, as well as chemokines. Giving Multikine before standard therapy for head and neck cancer — surgical resection followed by either radiotherapy or concurrent radiotherapy and chemotherapy — has been shown in phase II studies to increase tumour cell sensitivity to the radiotherapy. The cytokines recruit anti-tumour T-cells and other inflammatory cells, leading to a massive anti-tumour response. In particular, Multikine stimulates prolonged production of CD4-positive T-cells that infiltrate the tumour. The overall response rate in a phase II trial in 39 patients with advanced primary oral squamous cell carcinoma was 42% before standard therapy. The treatment had no toxic effects. The patients who responded to Multikine had tumours that were negative for the cell surface marker HLA (human leukocyte antigen) class II. Use of this marker might provide a way of selecting the patients that are best suited for treatment with Multikine.

The main endpoints for the phase III trial will be local-regional control of the disease, rate of disease progression and time of progression-free survival. Cel-Sci aim to launch the phase III trial globally and recruit about 500 patients in total.

WEBSITE http://www.cel-sci.com/products.htm

Homing in on sarcoma

Ecteinascidin-743 (ET-743) has shown activity in a phase II trial as a first-line therapy in patients with soft tissue sarcomas.

A total of 36 patients, many with bulky disease, were treated with ET-743 given as a 24-hour continuous infusion every 21 days. There was one complete response and five partial responses, with an overall response rate of 17.1%. The estimated 1-year progression-free survival rate was 21% and the 1-year overall survival rate was 72%. The main grade 3 and 4 toxicities were neutropenia and transaminitis.

ET-743 was synthesized more than a decade ago, having been found originally in extracts of the Caribbean marine tunicate *Ecteinascidia turbinata*. ET-743 selectively alkylates GC-rich regions of the minor groove of DNA. Even in preclinical studies ET-743 showed particular potency against soft tissue sarcoma cells. ET-743 has previously shown activity in phase II studies of patients with soft tissue sarcomas who had failed previous chemotherapy. This study confirms the activity of ET-743 and extends that activity to chemotherapy-naïve patients.

The activity shown in phase II studies is similar to that achieved with single agent doxorubicin or ifosfamide, or with combination therapy. Phase III randomized studies are ongoing.

ORIGINAL RESEARCH PAPER Garcia-Carbonero, R. *et al*. Ecteinascidin-743 (ET-743) for chemotherapy-naive patients with advanced soft tissue sarcomas: multicenter phase II and pharmacokinetic study. *J. Clin. Oncol*. **23**, 5484–5492 (2005)