Immunotherapy: Keyhole Limpet Hemocyanin

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Bropirimine below

Marketed in Europe since 1997 as an immunotherapy for non-invasive (Ta, T1 and CIS) bladder cancer and other purposes, this treatment is available to US citizens, limited to investigational use by Federal Law (21 CFR 50, 56, and 312).

Keyhole-limpet hemocyanin (immunocyanine) is a strong antigen/immunogenic compound being investigated as an intravesical agent. KLH is extracted and purified from the keyhole limpet mollusk, collected off the southern California coast. An average sized animal provides aproximately 5mg/ml hemocyanin and can be isolated in a relatively pure state from the hemolymph of the giant mollusks.1

The first clinical use of KLH in the immunotherapy of bladder cancer showing a decreased rate of recurrence after treatment was reported by Olsson in 1974.2

Lamm and associates compared KLH and Immucothel--a form of KLH modified for clinical use (Biosyn)-- in animal studies, and reported that the crude preparation of KLH offered greater antitumor activity than the purified KLH compound, although this has not been investigated in clinical trials.3 The team concluded that both crude KLH and Immucothel appear to be effective immunotherapies of use in the treatment of transitional cell carcinoma.4

Patients are first given an injection to evoke an immune response, followed by 18 monthly intravesical instillations in a saline solution. Jurincic reported that 95% and 86% of patients had complete response or downgrading, compared to 69% of patients in the study arm using Mitomycin C, indicating response rates comparable to BCG, though with less side effects. In a study which included 101 patients, three patients had low grade fever after the inital intracutaneous injection; however, no systemic toxicity or other adverse side effects were observed.1

KLH has been shown to produce a more predictable reaction than BCG, with similar results and less side effects.1 5

The best responders are CIS patients, which is a more difficult form of TCC to treat. In one study, of 19 CIS patients, 11 (58%) had a complete response. Ten (50%) of 20 patients with papillary TCC demonstrated a response, and 4 (33%) of the 12 patients with both forms of bladder cancer showed response.6KLH has been shown to be effective against tumor recurrence in bilharzial bladder with papillary TCC. Bilharzia is a form of bladder cancer caused by blood flukes (urinary schistosomiasis), which is mostly found in the tropics, and is the most common cause of TCC in Egypt. In such cases, KLH immunotherapy has been seen to reduce the recurrence rate to 15.4% compared to 76.9% before therapy.7

Although responses have been noted in patients with advanced disease, bulky tumors do not generally respond to immunotherapy.1 The advantage of KLH is its apparent lack of toxicity.3

More information about KLH

"Intracel"'s website, whose KLH product is called "BCI-ImmuneActivator". http://www.intracel.com/pdf/bci.pdf

The study protocol is/was: A Randomized, Multicenter Phase III Trial Evaluating the Efficacy and Safety of BCI-ImmuneActivator(tm) (KLH) Versus Adriamycin in BCG Refractory or Intolerant Patients With Carcinoma in Situ With or Without Resected Superficial Papillary Bladder Cancer (Summary Last Modified 10/2000) Protocol IDs: INTRACEL-BCI-9804-04

And Biosyncorp's Immucothel:

http://www.biosyncorp.com/bc_downloads/vacmune.pdf

Bropirimine for CIS

Bropirimine is an oral immunomodulator that has demonstrated anticancer activity in transitional cell carcinoma in situ (CIS) in both the bladder and upper urinary tract in a Phase II trial. Activity also has been documented in patients after prior therapy with BCG. Complete response was seen in 21 (24%) of 86 subjects. In 1998 Sarosdy and colleagues suggested that bropirimine may be an alternative to cystectomy for some patients with CIS who have failed or have not tolerated BCG.1

In earlier trials, bropirimine had been shown to be effective in treating approximately 50% of patients with carcinoma in situ (CIS). Ten (48%) of 21 evaluable patients had a negative ureteral cytologic analysis after 12 weeks (5 patients) or 24 weeks (5 patients). Of these 10 patients, 8 continued to have negative cytology for a period of 3 to 30 months (median, more than 9 months).2

Bropirimine shows promise with low toxicity in most cases, but further evaluation to improve responses and durability is warranted, and Phase III trials for CIS are now in progress.

Although most studies till now have been done on CIS patients, a 1998 study from Japan has shown the usefulness of bropirimine for use in superficial bladder cancer as well. Response rates of approximately 30% were seen in a study involving 17 patients. Adverse reactions were most commonly flu-like symptoms (70%), though all reactions were considered tolerable. The researchers concluded that bropirimine shows efficacy against marker tumors, has a good safety profile and oral activity, and may be useful for the prophylaxis of recurrence following transurethral resection of superficial bladder cancer.3

Although the results from newer intravesical therapies such as IFN, KLH, bropirimine, and PDT are encouraging, to date they have only proven to be useful in the therapy and prophylaxis of superficial TCC and long-term data on the prevention of recurrence, disease progression, and survival are unknown.4

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