A small portion of the patients receiving AraC experience painful enlargement of the salivary glands. In contrast to previous reports the two patients reported here experienced swelling and pain in both the parotid and submandibular salivary glands. Salivary glands enlargement occurred only in association with continuous infusion of standard dose of AraC and was not observed in the same patients after application of AraC in intermediate dose, in spite of the expectation that toxicity would be dose related.

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Low-dose BCG in Superficial Bladder Cancer With Strain Connaught Canada—as Effective as Strain Pasteur Paris?

D. Mack and J. Frick

Bacillus Calmette Guerin (BCG) intravesical therapy represents a major advance in the treatment of superficial transitional cell carcinoma (STCC) of the bladder. The high-grade stage T1 lesion (high-risk cancer) treated by transurethral resection alone is reported to progress to muscle invasion in 30 to 50% of patients. At present the optimal dose and treatment schedule remain to be defined, but treatment-related toxicity is significant. Therefore, as suggested by Pagano's group, we used BCG at a lower dose than previously reported, and also tested BCG Connaught Canada.

Therapy consisted of six weekly instillations of 75 mg BCG strain Pasteur Paris (3.75×10^8 colony-forming units, CFU) in 32 patients. Subsequently, the Pasteur strain was not available in Austria, and so another 25 patients entered into the study were treated with 27 mg BCG strain Connaught Canada (3×10^8 CFUs) to evaluate the feasibility, response and toxicity of BCG immunotherapy for patients with high risk STCC (Table 1).

Of 32 eligible patients in the Pasteur group, 84.4% had a complete response after the initial cycle with low-dose BCG and had stable disease. Similar results were achieved in the Connaught group: of 25 eligible patients, 84% had complete responses (Table 1). Mean follow-up was 30 months. Toxicity included profound local reactions, such as severe dysuria, frequency and gross haematuria. No systemic reactions except fever were seen; none of the patients needed INH (isonicotinic acid hydrazide). All reactions were treated symptomatically and were similar in both groups.

Table 1. Tumour stage/grade of 32 patients treated with BCG Pasteur and 25 patients treated with BCG Connaught in relation to response.

	Pasteur BCG		Connaught BCG	
Stage/grade	Response	No response	Response	No response
T1 II m	3	0	3	0
T1 II + TIS	4	0	1	0
T1 III s	0	0	3	0
T1 III m	11	1	9	1
T1 III + TIS	7	2	3	2
TIS	2	2	2	1
Total	27 (84.1%)	5	21 (84%)	4

m, multiple; s, solitary.

Morales and colleagues were the first to successfully use intravesical BCG for prophylaxis and therapy [1]. Later, Herr concluded that BCG produced a higher, more durable response rate than other intravesical agents and is the intravesical agent of choice for initial therapy of superficial bladder cancer [2]. BCG of various strains applied in different schedules yields a high response rate in STCC of the bladder [3].

However, the optimal dose of BCG treatment is presently unknown. In his first clinical trial of BCG, Morales and colleagues administered an arbitrary dose of 120 mg BCG Armand-Frappier [1]. This dose of 120 mg or an equivalent has been used by most investigators in subsequent studies. In 1988 Pagano and associates were the first to present results using a lower BCG treatment dose with the Pasteur Paris strain [4].

Akaza used BCG Tokyo 172 in a randomised study comparing an 80-mg dose with 120 mg [5]. All these studies clearly indicated that the lower dose of BCG was associated with decreased rates of both local and systemic side-effects. According to Pagano's results, we also used a low dose Pasteur BCG regimen in our STCC patients but we also used the Connaught strain. Until now, no data existed on the use of low-dose treatment with strain Connaught Canada. Mori and colleagues reported the effectiveness of BCG-Connaught with a total dose of 9.0×10^8 CFUs per instillation [6]. We used BCG-Connaught at one third of this dosage (3.0×10^8 CFUs). 21/25 patients showed response after the completion of the initial cycle. 4 patients did not respond and underwent more invasive therapy. None of our patients had tumour progression or metastasis. All patients showed irritative symptoms such as frequency, dysuria, gross haematuria.

This study suggests that low-dose BCG with strain Connaught Canada is as effective as low-dose BCG with strain Pasteur Paris. It is necessary to carry out several dose-finding studies with different strains. The fundamental aim of an adjuvant treatment-concept for STCC should be for maximum efficacy with the lowest morbidity and costs.

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Human Leucocyte Interferon-α Therapy can Induce a Second Response in Treatment of Thrombocytosis in Patients With Neutralising Antibodies to Recombinant Interferon-α2a

M. Merup, E. Törnebohm-Roche, K. Engman and C. Paul

INTERFERON-α (IFN-α) can effectively normalise thrombocytosis in polycythaemia vera (PCV) and essential thrombocythaemia (ET) [1]. IFN-α is an endogenous subtance with no leukaemogenic potential. It is an attractive therapy for younger patients since treatment with radioactive phosphorus and alkylating agents results in a highly increased incidence of acute leukaemia [2, 3].

Natural antibodies to IFN-α appear spontaneously without exogenous administration of IFN-α [4], but the most common trigger for formation of antibodies to IFN-α is treatment with exogenous IFN-α. Development of neutralising antibodies seems to be more common during treatment with recombinant IFN-α2a (rIFN-α2a) where frequencies between 20 and 29% have been reported [5, 6].

Interferon Alfanative® is a highly purified preparation of human leucocyte IFN-α that contains approximately 20 different IFN-α subtypes. During treatment with this drug no development of neutralising antibodies has been described [7].

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This is a report of 2 patients with PCV and ET complicated with elevated platelet counts who developed neutralising antibodies during treatment with IFN-α2a. After change of therapy to human leucocyte IFN-α, a second response to therapy could be achieved.

Case 1

A 68-year-old, previously healthy woman was admitted in December 1990 because of vertigo and vision disturbances. At diagnosis, a haematological analysis showed haemoglobin 200 g/l, erythrocyte volume fraction 66%, leucocyte count (LPK) 13.6 × 10^9/l, and a platelet count of 588 × 10^9/l. The blood volume was increased by 25%. A bone marrow aspiration

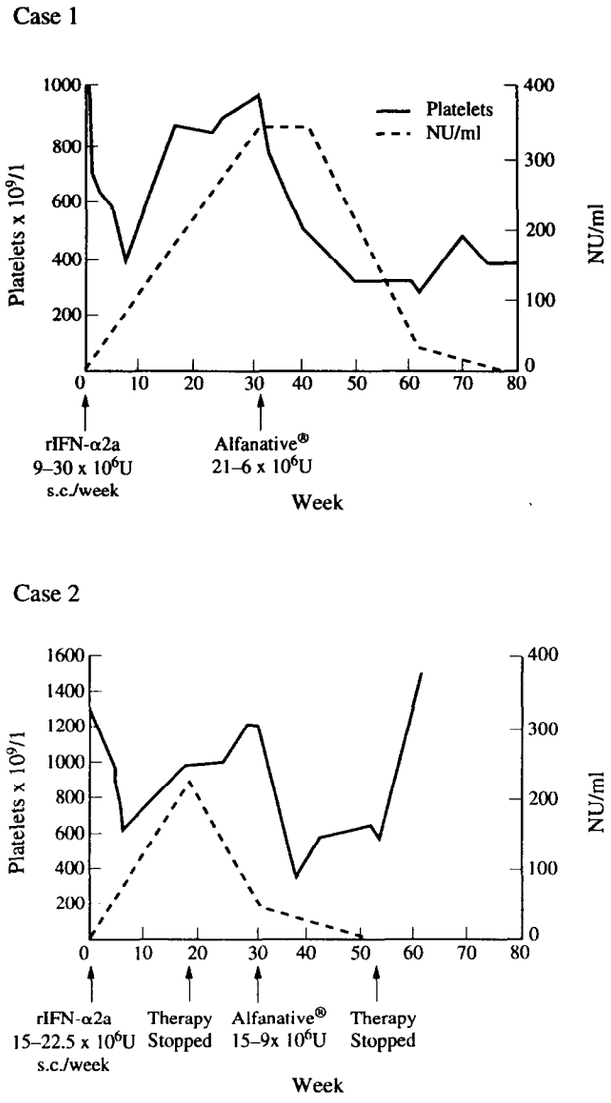

Figure 1. Platelet levels and titres of neutralising antibodies to rIFN-α2a in 2 patients with elevated platelets due to essential thrombocythaemia and polycythaemia vera. After initial response and subsequent treatment failure on rIFN-α2a, a second response was achieved after changing to human leucocyte IFN-α (Alfanative®). In case 2, treatment had to be discontinued due to induction of rheumatoid arthritis. The dotted line indicates neturalising antibodies to rIFN-α2a in neutralising units per ml.