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Feasibility of idiotype vaccination in relapsed B-cell malignancies

Feasibility of idiotype vaccination was statistically compared among five different B-cell malignancies in first relapse. When based on hybridoma production techniques, idiotypic vaccination for relapsed B-cell malignancies was consistently feasible only in follicular lymphoma patients, whereas the main cause of failure in other settings was the short survival of idiotype-producing hybridomas.

haematologica 2003; 88:1438-1440
(*http://www.haematologica.org/2003_12/1438.htm*)

With two ongoing, phase-III clinical trials enrolling newly-diagnosed follicular lymphoma (FL) patients, idiotypic vaccination[1] is approaching the final stage of its clinical development, that of demonstrating a possible benefit to patients. However, even in the event that either or both ongoing clinical trials succeed, a number of relevant questions would still remain unanswered, in particular whether idiotype (Id) vaccines may be feasible for most if not all relapsed FL and for some other B-cell malignancies.

An interim analysis was performed of all Id vaccine clinical trials currently ongoing at our institution based on a single, major endpoint, that is actual ability to administer an Id vaccine according to intention-to-treat. Inclusion criteria common to all cases were that the Id vaccine production attempt was carried out only at the time of pathologically-confirmed first relapse and that there was a prior, formal demonstration of the presence of a complete, clonal and tumor-specific immunoglobulin on the tumor cell surface. Furthermore, all Id vaccine production attempts were carried out by the same personnel and always using the same fusion partner (K6H6/B5, i.e. ATCC number: CRL-1823), according to the standard tumor/heterohybridoma fusion-based method previously described.[2-5] All patients received the chemotherapy regimen currently in use at our institution for their respective disease in first relapse (Table 1). Patients with FL, mantle cell lymphoma and small lymphocytic lymphoma were supposed to receive Id vaccine treatment if they achieved either complete (CR) or partial (PR) response, while patients with either diffuse large cell or Burkitt's lymphoma were supposed to receive Id vaccine treatment only if they achieved a CR.

Id vaccine treatment unfeasibility was evaluated as (i) related to induction treatment, if the salvage therapy did not induce a response sufficient to proceed with Id vaccination, (ii) fusion-related, if sufficient Id could not be generated to make the vaccine, or (iii) overall. Fusion-related feasibility was evaluated by taking into consideration both its potential causes of failure: short hybridoma survival and loss of Id production.

The feasibility of Id vaccination in relation to induction treatment was markedly different, being 80%-100% in indolent NHL subtypes and 40%-50% in aggressive ones. This difference was not, however, due to an overall lack of efficacy of the respective chemotherapy regimens, but rather to the different eligibility criteria for Id vaccination following chemotherapy. In fact, the overall response to induction treatment for aggressive NHL was 75%-80% (CR+PR), but in this group only patients achieving CR were considered eligible to receive Id vaccination. A far more important factor that halted treatment was Id-secreting hybridoma production (Table 2). Fusion experiments were successful in most FL cases at the very first attempt, whereas in other NHL cases, irrespective of the ultimate Id production outcome, as many as 5 attempts had to be carried out most of the time. Similarly, in most FL cases, the average number of successful fusion wells per 96-well plate was well above 15, whereas that of most of the other NHL cases was typically lower than five.

Statistically significant differences in fusion-related and overall feasibility were found between cases of FL and those of all other NHL, indolent and aggressive lymphoma, respectively (Table 2). Both fusion-related and overall feasibility of the Id vaccine treatment for FL in first relapse were comparable with those already described for both newly-diagnosed and relapsed patients with the same disease.[3-5] Interestingly, the Id vaccine production success rate was substantially low in cases of mantle cell lymphoma (MCL), as opposed to what has been preliminarily described with the very same method in newly-diagnosed MCL patients.[6] This apparent discrepancy could be due, at least in theory, to MCL cells at first relapse biologically resembling those of aggressive NHL rather than FL clones, with obvious possible repercussions on the fusion process.

Table 1. Induction treatment-related Id vaccine feasibility.

Diagnosis	*Number of patients*	*Induction treatment*	*Number of CR/PR*	*Induction treatment-related feasibility*
FL	15	CHOP×6	9/5	14/15 (93%)
MCL	5	R-HyperCVAD ×8	2/2	4/5 (80%)
SLL	5	FMC×6	4/1	5/5 (100%)
DLCL	5	mini BEAM×3 + BEAM + ABMT	2/2	2/5 (40%)
BL	4	mini BEAM×3 + BEAM + ABMT	2/1	2/4 (50%)
All but FL	19	See above	10/3 + 3	13/19 (68%)
MCL+SLL	10	See above	6/3	9/10 (90%)
DLCL+BL	9	See above	4/3	4/9 (44%)

Underlined CR and PR numbers refer to the cases for which subsequent Id vaccination was ethically acceptable according to the respective clinical trial protocols.

Table 2. Fusion-related and overall Id vaccine feasibility.

Diagnosis	*No. of patients*	*Fusion attempts median (range)*	*96-well plates median (range)*	*Successful fusion wells median (range)*	*Fusion-related feasibility*	*Cause of fusion failure (SHS/LIP)*	*Overall feasibility*
FL	15	1 (1-5)	10 (8-12)	186 (63-238)	13/15 (87%)*	1/1	13/15 (87%)*
MCL	5	5 (3-5)	15 (12-15)	65 (38-102)	2/5 (40%)	2/1	1/5 (20%)
SLL	5	5 (2-5)	15 (10-15)	66 (27-71)	1/5 (20%)	3/1	1/5 (20%)
DLCL	5	5	15 (10-15)	51 (29-62)	0/5 (0%)	5/0	0/5 (0%)
BL	4	5	15 (11-15)	53 (38-80)	0/4 (0 %)	4/0	0/4 (0%)
All but FL	19	5 (2-5)	15 (10-15)	57 (27-102)	3/19 (16%)*	14/2	2/19(11%)*
MCL+SLL	10	5 (2-5)	15 (10-15)	65 (27-102)	3/10 (30%)*	5/2	2/10 (20%)*
DLCL+BL	9	5	15 (10-15)	51 (29-80)	0/9 (0%)*	9/0	0/9 (0%)*

*Fisher's exact test with Bonferroni's correction was used to compare both the likelihood of a successful fusion and the overall feasibility of the treatment among patients with either FL or the remaining subtypes of both indolent and aggressive lymphoma. The level of significance required after this post-hoc correction was 0.025 (exact 2-tailed P). SHS: Short hybridoma survival. LIP: Loss of Id production. *p < 0.01.*

The main cause for Id vaccine production failure was poor hybridoma survival (15/18 cases), which accounted for 100% of failures in aggressive lymphoma (9/9 cases). Loss of Id secretion by growing hybridomas accounted for only 3/18 cases of Id vaccine production failure (Table 2).

All in all, our data suggest that, in the vast majority of cases, the feasibility of idiotypic vaccination for patients with first-relapse B-cell malignancies strictly depends on the ultimate ability to produe a viable Id vaccine rather than on the probability of inducing a clinical response suitable for subsequent idiotypic vaccination. In this respect, first-relapse FL clearly appears more suitable for hybridoma-based Id vaccine production than any other first-relapse NHL subtype tested in our laboratory.

As a major consequence of these data, clinical trials on Id vaccination for B-cell lymphomas other than FL in first relapse have been closed. However, it is possible that alternative methods to produce the Id protein, particularly those based on molecular techniques,[7-10] may prove far more efficient than the traditional approach we used in this study.

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Cell Therapy Area, Department of Hematology, University Clinic of Navarra and CIMA, Pamplona, Spain, on behalf of GEL/TAMO and PETHEMA

Funding: supported in part by: FIS Ministerio de Salud - RTIC Cáncer C03/10 (Madrid, Spain), Departamento de Educación y Cultura del Gobierno de Navarra (Pamplona, Spain), PIUNA (Pamplona, Spain), Ruzic Research Foundation (Beverly Shores, IN, USA). Maurizio Bendandi is a Leukemia and Lymphoma Society Scholar in Clinical Research. Financed in part by: FIMA Project (agreement between FIMA and UTE).

Key words: idiotype vaccine, feasibility, B-cell malignancies, hybridoma.

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Manuscript processing

This manuscript was peer-reviewed by two external referees and by an Associate Editor. The final decision to accept this paper for publication was taken by the Editors. Manuscript received July 3, 2003; accepted October 14, 2003.

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