Anti-Idiotype Antibodies in Cancer Treatment

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Abstract: Idiotypes, that is the collections of any immunoglobulin's specific epitopes, have been historically used in different ways for cancer treatment as immunotherapy tools. Inherently, the way they are actually employed mostly depends on the type of tumor cell target. The first such attempts consisted in the administration of monoclonal, anti-idiotype antibodies to patients with B-cell-lymphoma. They were able to show clinical activity, but were later abandoned due to both logistical constrains and the emergence of idiotype variants which could escape their action. Later, idiotype antibodies were also used as vaccines to stimulate the patient's immune system against the same type of tumors, a setting in which our group has provided the first formal proof of principle of clinical benefit associated with the use of a human cancer vaccine. Several approaches to enhance the efficacy of these idiotype vaccines have been described in recent years, some of them with encouraging results.

Meanwhile, new emerging immunotherapeutic strategies have been developed to target idiotypes mimicking idiotype-unrelated, tumor-associated or tumor-specific antigens displayed by several types of solid tumors. The results from those studies seem to support the concept of a decreased self-tolerance against these antigens when vaccination is successful. Of course, it remains of capital importance to better define what successful vaccination means. For instance, it is not clear whether the induction of an idiotype-specific humoral and/or cellular response needs to be documented to imply clinical efficacy or whether the latter may be achieved even when the former cannot be formally demonstrated. All in all, due to the wide application potential of idiotype-based immunotherapy, by means of this review we intend to cover both main achievements and open questions respectively obtained and still been faced by this experimental line of clinical research.

Keywords: Antibody, idiotype, immunotherapy, cancer, lymphoma, solid tumor, vaccine.

INTRODUCTION

The Idiotype

The idiotype is the set of idiotopes contained in an individual immunoglobulin (Ig) molecule (Figure **1**). Idiotopes are not to be confused with allotopes, the other type of antigenic determinants to be found in an Ig that can be identified by monoclonal antibodies (mAbs). Idiotopes can be found in the hypervariable regions of the Ig variable domains, as allotopes are mostly localized within the heavy- and light-chain constant regions of the Ig instead. Idiotopes are somatically generated, while allotopes derive from the inherited germ line. Finally, allotopes can be recognized as foreign because they are not shared by different individuals [1], whereas idiotopes can be recognized as foreign because of the minimum amount of them present in individuals is insufficient to induce self-tolerance. To date, the patient-specific idiotype is the best known, tumor-specific antigen for different B-cell lymphoma subtypes [2].

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Exploiting the Idiotype to Treat Cancer

From a theoretical standpoint, the most self-evident and straightforward exploitation of an idiotype as either a tumor-associated antigen (TAA) or a tumor-specific antigen (TSA) consists in targeting it by means of monoclonal antibodies (Figure **2**). In this case, the aim is to more or less directly kill idiotype-bearing tumor cells through passive immunotherapy. Less practical, and yet more refined, is instead the approach based on the administration to patients of a vaccine whose core is represented by the idiotype itself (Figure **3**). In this case, the scope of active immunotherapy is to stimulate the immune system to react in its own terms against the idiotype-bearing tumor cells. It goes without saying that either passive or active immunotherapy is substantially more tumor-specific, and as such with a lower toxicity potential, whenever the chosen idiotype is a TSA rather than a TAA. In general, an idiotype is a TSA when it is obtained from a B-cell lymphoma, while it is a TAA when it is found to be mimicking a certain solid tumor's idiotype-unrelated antigen. The main consequence arising from this categorization is that in the former case, irrespective of whether it is going to be used for passive or active immunotherapy purposes, the idiotype is not only tumor- but also patient-specific. Vice versa, in the latter case the same target may be present on the tumor cells of several patients. As such,

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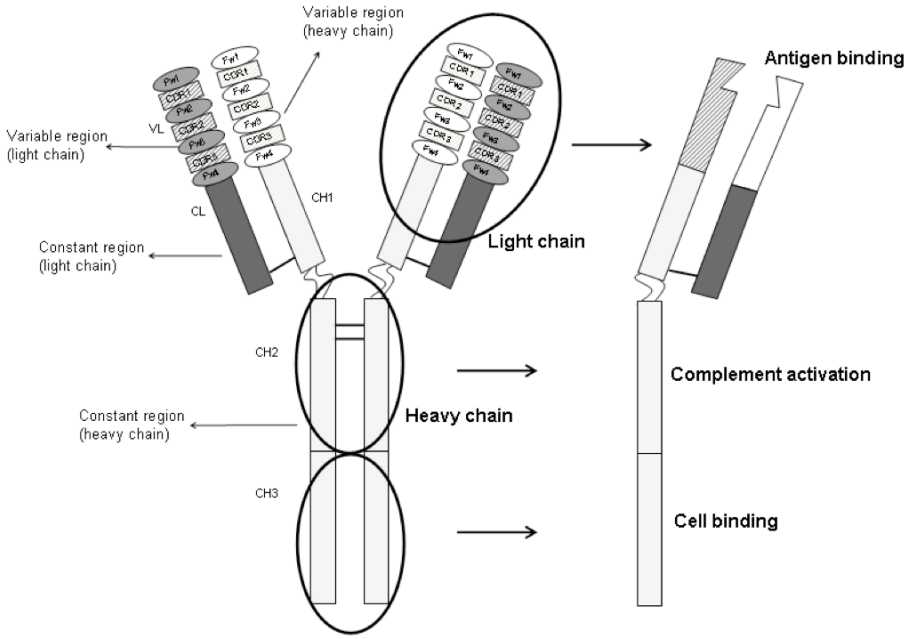

Figure 1: Schematic representation of the main structural and functional features of a typical immunoglobulin.

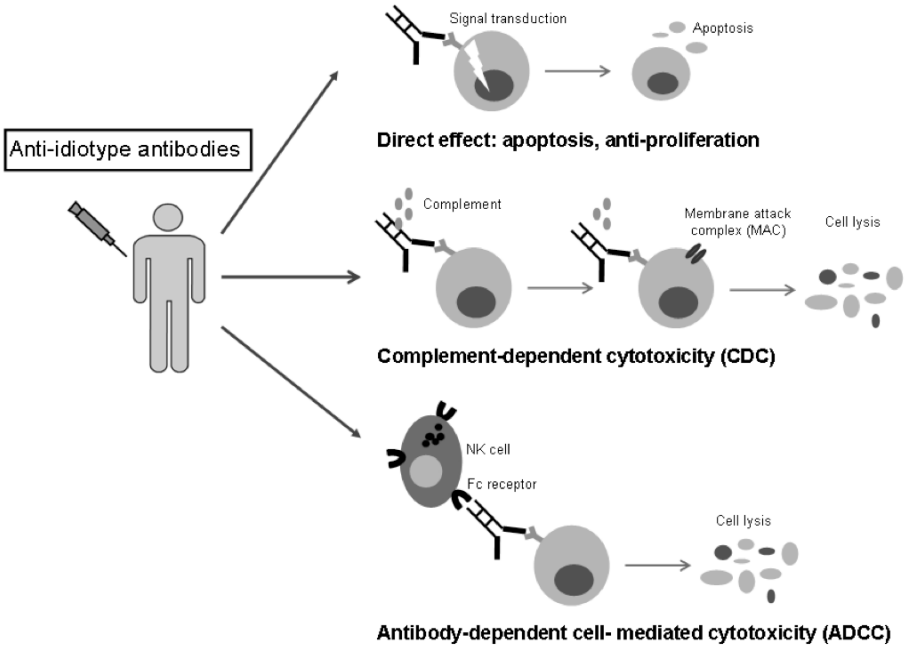

Figure 2: Potential anti-tumor pathways triggered by passive immunotherapy based on anti-idiotype antibodies.

each of the two overall strategies has to take into account substantially different problems in terms of business potential, large-scale production, logistics, science and social costs [3].

IDIOTYPE-BASED, PASSIVE IMMUNOTHERAPY

The first to report successful production and usage of custom-made, patient-, tumor- and idiotype-specific murine mAbs for the treatment of human B-cell lymphoma were Ron Levy and co-workers in 1982 [4]. In this pilot study, eleven patients were treated with such revolutionary products and a number of objective clinical remissions were reported, although some aspects remained to be optimized [5]. Similar results were later reported in even fewer patients by scientists at the University of Nijmegen [6]. However, in subsequent years both groups had to face the insurmountable problems associated with this exciting, fully-personalized strategy. In particular, passive anti-

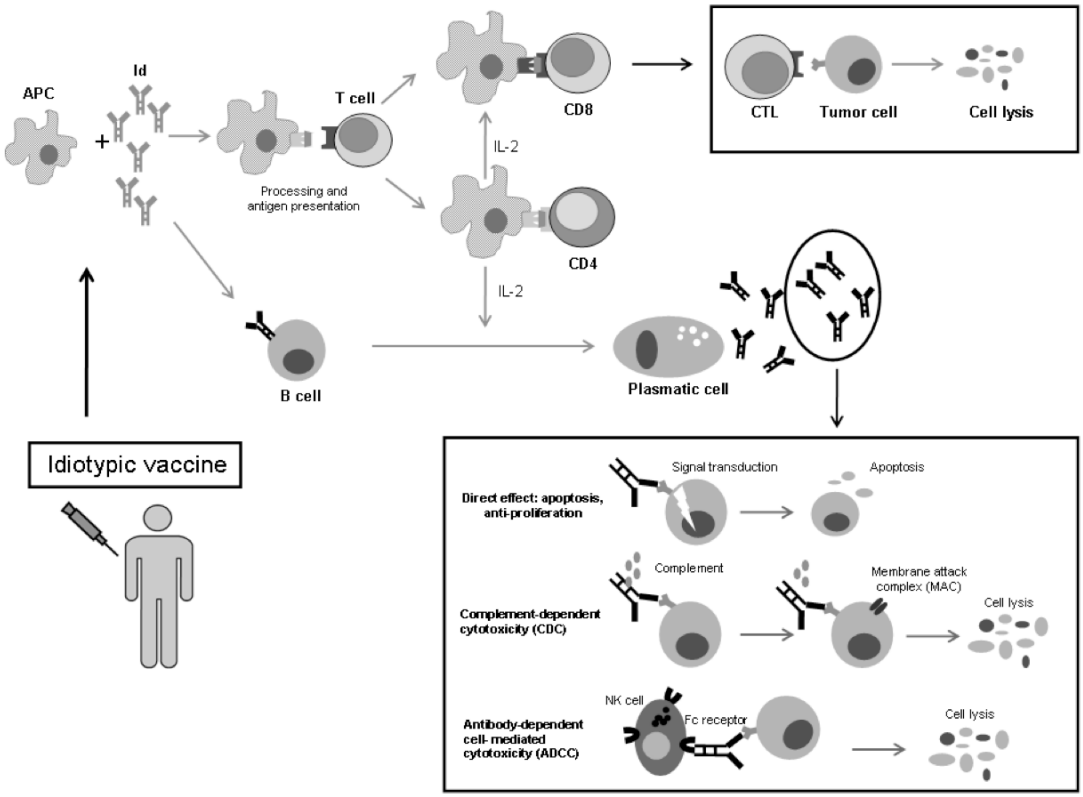

Figure 3: Potential anti-tumor pathways triggered by active immunotherapy based on anti-idiotype vaccines.

idiotype immunotherapy was incapable to eradicate the tumor clone in humans [7] and to prevent phenotypic and functional changes at tumor recurrence [8]. In other words, the extremely high specificity of murine anti-idiotype mAbs [9], that is the very reason of their potential success, might become a liability in case of lymphoma relapse with a modified idiotype. All in all, the emergence of idiotype-negative tumor-cell variants as well as that of idiotype variants escaping the customized anti-idiotype mAbs used previously, together with the unsustainable logistical problems associated with their productions, ultimately doomed the plan of using anti-idiotype mAbs as passive immunotherapy for B-cell malignancies on a large scale [3]. What was left of it, however, paved the way for the next step in idiotype research: to switch from passive to active immunotherapy in order to target B-cell lymphoma's idiotypes by means of a polyclonal, rather than monoclonal immune attack.

IDIOTYPE VACCINES FOR B-CELL MALIGNANCIES

Hybridoma-Derived, Soluble Protein Idiotype Vaccines

As it is true for passive immunotherapy based on anti-idiotype mAbs, it takes a complex effort to overcome the problems associated with providing a separate immunotherapeutic formulation to each patient [3]. However, a vaccine whose core is the whole idiotype itself has the potential to induce a polyclonal - therefore targeting several idiotopes -, humoral and/or cellular immune response capable of effectively eliminating the risk associated with the use of a mAb directed to a single idiotope. Once vaccination has elicited that polyclonal immune response, chances that idiotype mutations may over time abrogate most or all original idiotopes are virtually null [3].

Over the last two decades, three major scientific contributions have shown clear evidence of biological efficacy, clinical efficacy and clinical benefit [10] of idiotypic vaccination in a particular B-cell lymphoma subtype, that is follicular lymphoma [11]. It may be worth to note that all these proofs-of-principle have been obtained using the same overall vaccine formulation, whose core consists of the patient- and tumors-specific idiotype conjugated with an immunogenic carrier, keyhole limpet hemocyanin (KLH). First, at Stanford University Kwak and coworkers proved the biological efficacy of this peculiar type of active immunotherapy by demonstrating that most patients receiving their customized idiotype vaccine were able to mount an idiotype-specific

immune response, mostly of the humoral kind [12]. These results were subsequently expanded at the same institution [13-15]. In addition, pulsing autologous DCs with the soluble, tumor-specific idiotype protein [16] allowed similar conclusions to be drawn, but did not demonstrate improved biological and clinical results as to warrant further development [17]. The second major breakthrough originated from a clinical trial conducted at the National Cancer Institute and based on an idiotype vaccine formulation including for the first time granulocyte macrophage colony-stimulating factor (GM-CSF) as an immunologic adjuvant [18]. The results of this study clearly showed the clinical efficacy of idiotypic vaccination, since in most patients with detectable minimal residual disease after chemotherapy completion the demonstration of a vaccine-induced, idiotype-specific humoral and/or cellular response was associated with persistent clearance of the minimal residual disease itself [19]. Similar results were later reproduced by another group in Spain [20]. Finally, six years ago the first evidence of clinical benefit associated with the use of idiotypic vaccination was provided through a clinical trial conducted at the University of Navarra Hospital. In particular, all patients with follicular lymphoma in second complete response after standard chemotherapy without rituximab who developed a vaccine-induced, idiotype-specific humoral and/or cellular immune response experienced a second complete response statistically significantly longer than their respective first complete response previously obtained through chemotherapy with or without rituximab [21]. Vice versa, all patients in the same situation but who failed to develop such an immune response experienced the typically shorter second complete response as compared to the corresponding first [21]. The same group also showed that idiotypic vaccination can be safely administered over several years without interruption and with systematically negligible toxicity [22].

After clearing all major proof-of-principle hurdles, idiotypic vaccination reached the stage of large-scale, randomized clinical trials in order to possibly obtain regulatory approval and become available to the general B-cell lymphoma patient population. Unfortunately, all three such clinical studies failed to achieve that ultimate goal. Both in hindsight [10] and before their respective data were unblended [23], it was relatively easy to note that each clinical trial either featured crucial study design pitfalls or experienced serious enrollment problems. Be as it may, beside the failure in winning vaccine approval itself, the worst outcome consisted in the fact that it was not possible to fully evaluate the potential of each trial's vaccine per se. In other words, any or all of the three types of idiotype vaccines used in these studies may have been effective products, and yet the trial design or some other circumstances may have prevented them to prove such a possibility [24, 25].

The sole idiotype vaccine randomized clinical trial based on hybridoma-derived idiotypes [10] was launched over ten years ago and lasted nearly a decade [26]. Nevertheless, it only managed to complete a third of its required accrual. Overall, the study showed barely statistical significance in terms of relapse-free survival favoring vaccinated over control patients. Moreover, it also retrospectively showed that patients with an IgM-borne idiotype clearly benefitted from vaccination, while those with an Ig-borne idiotype did not [27]. As for the general conclusion of the study, that is that idiotypic vaccination is better than placebo to prevent follicular lymphoma relapse, the main problem is that the minimal statistical significance has been obtained in a severely-reduced patient casuistry. Therefore, we do not know whether a complete patient accrual would have confirmed, enhanced or erased such feeble and yet positive result. Concerning the intriguing finding suggesting that the idiotype-bearing Ig's isotype might influence the idiotypic vaccination clinical outcome, it is worth to make a couple of considerations. First, hybridoma-derived idiotypes are mounted on the same Ig scaffold as that of the original tumor Ig, while in the case of recombinant idiotype vaccines, the scaffold is the same for all patients and is not meant to reproduce that of each patient's tumor Ig. Second, after learning of this finding, both we and others retrospectively reviewed our entire casuistries of patients ever vaccinated with hybridoma-derived idiotype vaccines and were unable to appreciate any immunological and clinical outcome difference between cases featuring an IgM- or an IgG-borne idiotype. Indeed, this aspect as well as that concerning whether a humoral or a cellular immune response may be more worth pursuing through idiotypic vaccination to achieve clinical benefit remain hot topics to be addressed in the future.

Recombinant, Soluble Protein Idiotype Vaccines

Given the potential logistical and technical shortcomings of hybridoma-derived idiotype vaccine production [28], other groups have attempted to better streamline it by means of recombinant technology [29].

For instance, at Stanford University a personalized vaccine based on idiotypes elaborated by transfected mammalian cells has been used in follicular lymphoma patients both in a phase I/II and a randomized clinical trial. The former study showed the safety of the approach, its ability to elicit idiotype-specific immune responses and an encouraging median progression-free survival of 38 months [30]. The latter study, concluded in 2007, has not yet been published, though some of its findings have been discussed in a different, peer-reviewed work which in turn described the clinical results of the last randomized clinical trial on recombinant idiotypic vaccination ever launched [31]. In this case, however, the recombinant idiotype was produced by insect rather than mammalian cells [32].

All in all, both of these two randomized clinical trials completed their accrual but failed to show statistically significant different clinical outcome between patients receiving the bona fide vaccine and those to whom a control product was administered. As mentioned above, however, a number of substantial pitfalls in each trial's study design may have contributed to or even fully caused their failure [10, 23].

Finally, it is worth mentioning other methodological approaches designed to possibly improve and/or simplify the production of recombinant idiotypes. Since the overall list would probably exceed the scope of this overview, we will limit it to the experimental products that have reached at least the stage of early clinical trials. In this respect, a conspicuous amount of work has to be credited to the group at the University of Freiburg [33, 34]. Briefly, recombinant idiotype vaccines produced in bacteria and based on the tumor-specific Ig's Fab have been able to elicit idiotype-specific immune responses in lymphoma patients, and these results have been often associated with an excellent progression-free survival and even with some long-lasting remissions [35]. Our own experience with recombinant idiotype vaccine started only few years ago in a collaborative effort to exploit plant-based technology to rapidly and cost-effectively produce customized idiotypes for lymphoma patients. The preliminary results are encouraging [36] and a phase-I clinical trial is currently ongoing in the United States.

DNA-Based Idiotype Vaccines

Over the last five years, no tangible progress has been made in the attempt to bring to clinical trial fruition an alternative strategy to immunize lymphoma patients against their tumor-specific idiotype, that of DNA-based idiotypic vaccination. In the previous decade, a conspicuous amount of work had been carried out in this respect, particularly by scientists at the University of Southampton [37, 38] and at Stanford University [29]. The idea of injecting in form of DNA sequence both idiotype and adjuvant and have the host cells producing both proteins *in vivo* is extremely intriguing and would avoid most of the time-consuming and laborious processes associated with the production of customized, soluble protein idiotype vaccines. However, it is possible that the recent failures of large-scale, randomized clinical trials to deliver regulatory approval for soluble protein idiotype vaccines, with the large amount of funds lost in each of them, may have somewhat increased the tendency to risk aversion even with respect to DNA-based idiotype vaccines.

Idiotype Vaccines for Multiple Myeloma

Over the last five years, a number of groups have tried to revive the interest in idiotypic vaccination for the treatment of multiple myeloma. As reviewed before [3], it is not clear why the results obtained by this approach in myeloma patients have been so dramatically inferior to those achieved in B-cell lymphoma. It certainly does not depend on the competition with alternative treatments, as this phenomenon is equally fierce in both settings. From a different perspective, myeloma is a generally more aggressive disease than indolent lymphoma, but it is also a pathological condition in which the patient- and tumor-specific idiotype may be obtained far more easily and rapidly than in any lymphoma [39]. It has been speculated that this very last feature, which depends on the fact that large amounts of idiotype may be actually freely circulating in the blood and secreted in the urine of myeloma patients, may make the patient's immune system less likely to be stimulated by and harnessed against this dominant self-protein [2].

Be as it may, it has to be observed that the combined modality treatment sequentially including autologous stem cell transplant and idiotypic vaccination [3] seems to have been abandoned. Instead, we have tried, unsuccessfully, to ascertain whether donor idiotype immunization prior to reduced-intensity conditioning, allogeneic stem cell transplant, followed by post-transplant idiotypic vaccination of the recipient could exert some clinical benefit. In particular, we noted that nowadays most if not all patients undergoing allotransplant do so later in the course of their disease compared to previous years. As such, they tend to reach transplant stage being heavily

pretreated, severely ill and/or prone to suffer important transplant complications. Moreover, owing to regulatory limitations, in our trial we were not allowed to use GM-CSF in the donor vaccine formulation, which was therefore limited to the remaining two ingredients of the traditional idiotype vaccine, that is sibling patient's idiotype and KLH. All in all, both accrual and results were demoralizing and the trial was brought to an early conclusion [40].

Outside the transplant setting, one of the most active groups in the field of multiple myeloma idiotypic vaccination, that of Karolinska Institute, has clinically tested an idiotype vaccine whose formulation excludes KLH, retains GM-CSF and adds interleukin-12. The results appear to be encouraging and warranting research in larger scale trials, as their findings indicate a possible correlation between induction of idiotype-specific T cells and reduction of circulating, clonal myeloma cells in most patients [41].

Finally, a recent contribution has somewhat renewed the interest on a relatively well known manner to deliver idiotype vaccines to patients: idiotype-pulsed dendritic cells (DCs). In particular, Yi *et al.* immunized multiple myeloma patients with intranodal injections of CD40 ligand-matured, idiotype-pulsed DCs, eliciting specific T-cell responses in most cases, observing negligible toxicity and maintaining stable disease in half of the patients over half a decade [42]. It remains to be seen whether, based on these results and taking into account the laborious procedure of performing intranodal injection, this novel version of an old immunotherapeutic strategy will be expanded into large clinical trials.

ANTI-IDIOTYPE ANTIBODIES AS AN IMMUNOTHERAPY FOR SOLID TUMORS

Clinical Works

The general antigen mimicry principles on which bona fide idiotypes can be used to harness the power of a patient's immune system against a non-lymphoid tumor antigen have been extensively reviewed by others [43]. Similarly, several attempts to bring this type of immunotherapy to the fruition of cancer patients affected by melanoma, colorectal, ovarian and breast cancer have been also reviewed by us [3]. All in all, these principles make possible to target tumor antigens that have no functional association with any immunoglobulin as a whole or with its idiotype in isolation.

Over the last five years, however, despite dozens of basic and preclinical reports concerning the potential usefulness of anti-idiotype immunotherapy in oncology, the number of trials whose results have been actually reported has disappointingly shrunk to just one. All the more reason, it is worth mentioning the commendable effort by Soriano and coworkers to treat breast cancer patients by means of this therapeutic approach [44]. This group investigated feasibility, safety and potential efficacy of a metronomic combination of low-dose chemotherapy and therapeutic vaccination for the treatment of patients with metastatic breast cancer who have become resistant to conventional chemotherapy. In a formal clinical trial, twenty one patients with disease progression were treated with metronomic chemotherapy, consisting in 50 mg of cyclophosphamide orally daily and 2.5 mg of methotrexate orally bi-daily, combined with five bi-weekly subcutaneous injections of 1 mg of aluminum hydroxide-precipitated 1E10 anti-idiotype mAb. Following the ten overall immunizations, vaccine boosts were also administered once a month. From a clinical standpoint, five patients achieved an objective response, eight showed stable disease and eight did not respond to the combined modality treatment. Median time to progression was about ten months, while the median overall survival time was about thirteen months. Overall, the median duration of any response, that is combining complete and partial response with stable disease cases, exceeded eighteen months, with more than three quarter patients maintaining the best clinical result longer than a year. Major side effects were never observed. Given the potential impact on the survival of poor prognosis patients with metastatic breast cancer, the simple administration and the mild toxicity profile, this combined modality treatment may warrant further clinical investigation. However, the only way to ascertain the actual contribution of idiotype vaccination to the clinical results, it would be necessary to randomize patients into two treatment arms, one based on the combined modality treatment, the other based only on the same low-dose, metronomic chemotherapy.

CONCLUSIONS

Anti-idiotype mAbs used as a passive form of immunotherapy for B-cell malignancies have shown to be safe and quite effective, but have not been developed into a widespread multicenter application owing to the difficulties in production and to the narrowness of their specificity. Vice versa, patient- and tumor-specific idiotype vaccines, though equally

complicated to produce, whenever effective assure the induction of a polyclonal, more comprehensive, idiotype- and tumor-specific, both humoral and cellular immune response. Most of such a polyclonal immune response is likely to remain effective against any idiotope persisting even in case parts of the idiotype may later undergo replacing mutations, while the effectiveness of a mAb could be entirely abrogated, should its targeted idiotope be lost through those mutations. Moreover, the administration of such vaccines is associated with negligible toxicity in all cases and with clinical activity in practically all patients who respond to it from an immunologic standpoint. Of course, research in this field will still need to be led by the interest in lymphoma immunotherapy. However, if major breakthroughs will be delivered in some of these B-cell malignancies, there is little doubt that anti-idiotype treatment of some solid tumors through TAA idiotype mimicry will resume being explored with more enthusiasm.

While the last decade featured the surge and fall of a number of hyped, large-scale, randomized clinical trials on lymphoma idiotypic vaccination which were often set up too hastily, focusing more on competition that on sound clinical trial designs, in a round-the-clock competition among themselves, it is likely that the next decade will see an excessively cautious approach towards this therapeutic strategy dominating the scene. The several hundred million dollars wasted in the former timeframe are indeed likely to heavily weigh against other such investments to be poured lightly into the latter. Yet, idiotypic vaccination remains as promising now as it was ten years ago, before poorly-designed or poorly-conducted phase-III clinical trials had a chance to actually backfire.

Indeed, three overall failures in as many randomized clinical trials, together with positive results from large-scale studies on alternative therapeutic solutions openly competing with idiotypic vaccination have inevitably contributed to create an environment that is certainly unfavorable towards idiotype vaccines. This situation evidently draws a sharp contrast with what the trend was only ten years ago, when nearly any oncologist either hoped or sincerely believed that, by now, cancer vaccines would be part of the gold standard therapeutic strategies for many malignancies. Whether this fall in conceptual acceptance of idiotypic vaccination may lead to a recovery of the whole strategy or just to its demise will mainly depend on the development of novel, even more powerful - and still non-toxic - vaccine formulations, in which together with an easy methodology to *in vitro* recover the tumor idiotype, better adjuvants may have a chance to enhance idiotype immunogenicity.

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