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Improving the chance of cure of follicular lymphoma by combining immunotherapy and radioimmunotherapy based on anti-CD20 antibodies?

The recently published ESMO lymphoma treatment guidelines [1] recommend the use of single-agent rituximab as an option in follicular lymphoma (FL) for avoiding the side-effects of chemotherapy. We may add to this point that results from the literature as well as our own observation show that radiolabeled anti-CD20 radioimmunotherapy (RIT), as a treatment consisting of two injections given at a 7-day interval, can lead to high rates of complete responses (CRs) and over 10 years recurrence-free survival in a significant percentage of patients. These results, confirmed at the molecular level in a high percentage of cases, were observed with treatment at first line, in consolidation and in relapsed/refractory indolent lymphoma [2–4]. They favorably compare with the above-mentioned results of single-agent rituximab [1] shown to induce long-term remissions of FL and to represent a well-tolerated maintenance therapy [5].

Surprisingly, these two very efficient forms of B cell-specific anti-CD20-mediated therapies have never been tested in combination in a well-designed clinical trial of FL. In the most recent randomized, phase III trial of untreated FL, RIT, and rituximab treatments were compared, but they were both associated with the same combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy [6]. The two arms gave excellent and similar results, but the two antibody-mediated therapies could not be evaluated individually or in combination.

The combination of these two forms of anti-CD20 immunotherapies might increase the CR with less side-effects than chemotherapy and preserve the T cells' immune defenses.

Indeed, the positive role of T cells' responses against lymphomas has been well documented in experimental and clinical investigations, including idiotype vaccination and allogeneic bone marrow transplantation [7]. Furthermore, the fact that the two approved anti-CD20 antibodies, tositumomab and ibritumomab, are of murine origin includes tumor targeting of new antigens, which can be recognized in their processed form by the patient's T lymphocytes [8]. The important role of effector cells from innate immunity, such as natural killer (NK) cells, is well known both for antibody-dependent cell mediated cytotoxicity and for the prevention of recurrence. Interestingly, it was recently shown that injection of rituximab resulted in the activation of the NK cells in patients with the high-affinity Fcγ receptor genetic polymorphism [9].

The strong efficacy of RIT cannot be entirely explained by the relatively low radiation dose to the tumor cells or by the associated administration of unlabeled anti-CD20 antibody, but probably by the combination of both that associate with the patient's preserved T cells immunity. It has been recently reported that irradiated lymphoma cells have an increased immunogenicity and that irradiation of lymphoma, accompanied by systemic delivery of a TLR7 agonist, can induce durable antitumor immune response in murine syngeneic lymphoma models [10].

In conclusion, we think that in FL the combination of these two antibody-mediated biotherapies might produce a synergy leading to higher CRs and longer disease-free survival rates than each single modality and, thanks to the preservation of the patient's immune system, improve the chance of cure.

F. Buchegger[1,2*], J.-P. Mach[3], O. W. Press[4], A. Bischof Delaloye[5], S. M. Larson[6], J. O. Prior[1] & N. Ketterer[7]

[1]Department of Nuclear Medicine, Lausanne University Hospital, Lausanne
[2]Department of Nuclear Medicine, Geneva University Hospitals, Geneva
[3]Department of Biochemistry, University of Lausanne, Lausanne, Switzerland
[4]Department of Medical Oncology, University of Washington Medical Center, Seattle, USA
[5]Faculty of Medicine, University of Lausanne, Lausanne, Switzerland
[6]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, USA
[7]Clinic Bois-Cerf, Onco-Hematology, Lausanne, Switzerland
(*E-mail: franz.buchegger@chuv.ch)

disclosure

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Spin and bias: the tip of the iceberg

Vera-Badillo et al. [1] have to be congratulated for uncovering a problem with reporting of trial results, a problem that distorts the record, impedes inference, and can lead to flawed medical decisions. It is important to note that the associated problems of biased reporting and spin remain problems no matter how often they occur; once is once too often.

Hence, the proportions presented should be understood in this context, and we should not lose sight of the forest for the trees. Nevertheless, I would propose that the proportions presented should have been based on the subset of 30 trials with complete information (including the primary end point that was prospectively specified), either instead of or in addition to the proportions that were presented based on the full sample of 164 trials.

We are told, for example, that 7 of the 30 trials reported a different primary end point, and we can only imagine that this switch would have occurred in a higher proportion of the other 134 trials, given that the authors of those trials did not need to worry about getting caught. This uncertainty undermines our ability to offer credible statements about how often these 134 trials were biased or spun. But we do see bias in at least 7 of the 30, and have to wonder how often there was bias and/or spin in the other 23 among these 30. This would be a rather telling statistic, arguably more telling than the one based on the full set of 164.

Moreover, the problems reported, though certainly of substantial importance, may still represent only the tip of the iceberg, and not only because we can check for changes in the primary end point in only 30 of the 164 trials. Beyond this, we also have the fact that there are many more biases, far too many to list here, that may have gone into producing spurious statistical significance in the primary end point. So what we have here is a best-case scenario, and a comprehensive look at spin, plus bias as defined here, plus bias defined more broadly, might reveal a far worse state of affairs in the trial research record [2].

V. W. Berger*

Biometry Research Group, National Cancer Institute, and UMBC, Bethesda, USA
(*E-mail: vb78c@nih.gov).

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Spin and bias: the tip of the iceberg

We thank Dr Berger for his kind comments on our study [1]. Our primary aim was to determine the frequency of spin and bias applied to misreporting the primary end point, and failure to include a description of toxicity in the abstract. To focus the findings of our research on only 30 trials with complete reporting of the primary end point (only 18% of the total sample) would perhaps have allowed us to separate spin (i.e. where complete information is provided but results are presented in such a way as to make them appear to be more favourable to the