Review

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Challenging paradigms in lymphoma treatment

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Introduction

Among the several merits that must be ascribed to the Revised European–American Lymphoma (REAL) classification [1], the most relevant from a therapeutic standpoint is that it has ultimately allowed clinicians all over the world to fully compare the results of clinical trials conducted elsewhere. Therefore, it is not surprising that it was included almost untouched within the current WHO classification of Tumours of Haematopoietic and Lymphoid Tissues [2]. All previous lymphoma classifications had failed in this scope, mainly owing to the different language and concepts used by pathologists and clinicians in different countries to refer to the variegate panorama of lymphoid tumors.

Meanwhile, the continuous effort towards the refinement of lymphoma patients' prognosis systems has also succeeded in elaborating new and better prognostic indeces, such as the International Prognosis Index (IPI) [3] and, perhaps, the more recent Follicular Lymphoma International Prognostic Index (FLIPI) [4]. It is indeed expected that the better categorization of patients, which is intrinsic to the systematic and broad use of these scores, will help to reach higher overall cure rates by calibrating disease treatment to the real needs of the individual patient. In this respect, the concomitant effort to objectively combine 'traditional', biological and clinical prognostic factors with the astonishingly attractive findings of lymphoma genome profiling [5, 6] seems to represent another crucial step towards improving the process of selecting the best possible treatment. Of course, this ongoing effort might even confuse the whole scenario of lymphoma management in the short-term, but the ultimate hope is that it will prove invaluable in clarifying a number of concepts. Among them for instance, in a time of rapidly aging population, the concept of the 'elderly patient' is still too vague, undefined and often neglected.

Over the last two decades, it has become increasingly clear that intensified treatment does not necessarily translate into better clinical results. In particular, the unique goal to be pursued should remain that of curing as many patients as possible with as little treatment as possible. However, this lesson has apparently only been applied dose- and field extension-wise to radiation treatment (RT), whereas the same attention has not always been given to chemotherapy (CHT) dose intensity reduction. This fact, aside from the obvious issue of short- and long-term toxicity in general, has generated paradoxical situations such as that of Hodgkin's disease (HD) and follicular lymphoma (FL). In the case of the highly curable HD, aggressive CHT regimens [7–9] have erased the significance of any prognostic factor at diagnosis [10, 11], while increasing both the overall toxicity and the second neoplasm frequency, without abolishing in principle the risk of progression, resistance or relapse. The only logical conclusion that can be drawn from these facts is that, currently, an important fraction of HD patients may be overtreated [12]. On the other hand, in the case of the substantially incurable FL, the number of treatment options and the tendency towards chemotherapy intensification [13–17] have led to a confusing situation where a number of patients are also possibly either over or poorly treated, without a clear-cut improvement in either cure or survival rates.

An important area of both new hope and concern is the growing number of biological therapies that have come into their own. Among them, passive, active, adoptive and radio-immunotherapy share great promise and raise important questions in terms of appropriateness of their clinical use. It will be advisable to study carefully their effective applications to lymphoma treatment, in order to possibly avoid the unfortunate experience with α-interferon, which paradoxically is still used in individual patients, but is kept out of most clinical trials.

All in all, both the recent and the expected further findings in lymphoma classification, prognostic systems and treatment options justify being optimistic of a substantial improvement of the already relatively satisfactory results achieved in lymphoma management.

Hodgkin's disease

Currently, the major management issues related to HD concern the treatment options for patients presenting with the following: stage IA, stage IB and II, stage III and IV, elderly age, residual mediastinal lesions, and relapse or resistance. In addition, nearly

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half a century after the first HD cases were cured by RT alone, the exact role of this treatment option is now, more than ever, under intense scrutiny.

Over the last couple of years, at least four studies have been conducted and published, while others have been started, in order to possibly contribute to the clarification of the way a patient should be treated at diagnosis, mainly depending on the Ann Arbor stage only.

Press et al. [18] have randomized as many as 348 patients with either IA or IIA, supradiaphragmatic HD to receive either subtotal lymphoid irradiation (STLI) or three cycles of doxorubicin- and vinblatine-based CHT plus STLI. Response-wise, the latter treatment option proved dramatically superior in terms of both failure-free survival (94% versus 81%) and relapse rate ($P < 0.001$). However, the relatively short follow-up time (3.3 years) does not allow a complete assessment of other parameters, such as overall survival (OS) and long-term toxicity.

In Germany, Sieber et al. [19] randomized 996 patients with stage I–III disease (excluding those in stage I–II with no risk factors) to receive, in combination with extended-field RT, either rapidly alternating COPP/ABV/IMEP or conventional alternating COPP/ABVD. With a median follow-up time of 7 years, no differences at all were found in terms of complete responses (CR = 94% versus 93%, respectively), freedom from treatment failure (79% versus 80%, respectively), OS (88% in both arms) and second neoplasm frequency (22 events in both arms), or serious infections and toxic deaths.

Horning et al. [8] recently updated the results of their prospective clinical trial on the use of Stanford V CHT regimen plus RT (on bulky sites only) for HD patients with either stage I–II with bulky mediastinal mass presentation or stage III–IV. With a median follow-up of 5.4 years, the 5-year freedom from progression (FFP) was 89% and the OS was 96%, with a highly significative difference in terms of FFP for the patients with prognostic score [10] <3 (94% versus 75%, respectively; $P < 0.0001$). Considering also that no secondary leukemia has occurred yet, as many as 46 pregnancies have been recorded instead ever since and the freedom from second relapse for the 16 relapsed patients was 69%, high expectations suggest the ongoing Intergroup trial (E2496) randomizing HD patients should receive either standard ABVD or Stanford V (both with and without RT).

In fact, a recent preliminary report, characterized by an unexpectedly low response rate of HD patients to the Stanford V regimen, is further confusing the scenario. Levis et al. [20] randomized 355 advanced stage (IIB–IV) HD patients to receive standard ABVD, Stanford V or MOPP/EBV/CAD (MEC), each followed by RT on residual and/or bulky disease sites. At the most recent interim evaluation, as many as 272 patients were evaluable (ABVD = 98; MEC = 83; Stanford V = 91), and the main clinical features were well balanced among the three groups. The CR rates (CR + unconfirmed CR) were 70%, 71% and 58%, respectively, prior to RT and 89%, 92% and 73%, respectively, following RT completion. In both cases, ABVD and MEC showed better results ($P < 0.01$) than Stanford V. Furthermore, MEC proved significantly more toxic than the other two CHT regimens.

Finally, Radford et al. [21] randomized 282 HD patients either in stage I–II (with bulky mediastinal presentation and/or B symptoms) or III–IV to receive either ChlVPP/EVA or VAPEC-B (both followed by RT on residual and/or bulky disease sites). With a median follow-up time of 4.9 years, the superiority of the former CHT regimen has been rapidly and clearly demonstrated in terms of 5-year FFP (82% versus 62%, respectively), event-free survival (EFS = 78% versus 58%, respectively) and OS (89% versus 79%, respectively). However, it appears that, in the subset of patients with prognostic score <3, the two regimens are equivalent.

All in all, these data seem to once again point out that when treating HD patients, a little more attention should be paid at diagnosis to their prognostic factors than only to the highest CR rates achieved by each CHT regimen. Otherwise, the risk of paying too high a global price for overtreatment appears to be excessive. In addition, the same concept should be applied to limiting the use of adjuvant RT in both early and advanced stage HD [12].

In general, it is far from unreasonable to treat HD patients presenting in stage IA without unfavorable prognostic factors with RT alone. Likewise, patients presenting with stage IB–II disease may be well treated with ABVD plus RT on residual and/or bulky disease sites only. On the other hand, the quest for the best possible treatment for HD patients presenting with stage III–IV disease is far from over. Save the BEACOPP [7] regimen, which is however characterized by higher short- and long-term toxicity [22], no other CHT schema has yet proved to be superior to the ABVD regimen. Therefore, other randomized trials such as the above-mentioned E2496 are warranted.

As for the treatment of elderly patients with HD, the lack of clear-cut data from randomized trials, as well as the difficulty in establishing a common ground about the age limit past which a patient should be considered elderly, mean that each group's experience ends up having some, but not much, scientific merit. In our experience, the VBM regimen [23], eventually followed by RT on residual and/or bulky disease sites, is reliable and relatively efficacious for HD patients above the age of 65 years.

The diagnostic management of residual mediastinal lesions following HD treatment has recently been revolutionized by the advent of [^{18}F]fluorodeoxyglucose positron emission tomography (FDG PET). The very few [24] or even absent (our unpublished data) cases of false-negative FDG PET reported, together with the equally lower and lower number of false-positives [24] and the greater experience being gained by FDG PET specialists, are setting the stage for whole-body FDG PET to become a fundamental tool in HD patient management. In particular, its role in association with computed tomography scans seems to be pivotal in the restaging of patients with mediastinum and abdomen bulky disease presentation. In this setting, that is following CHT with or without RT, its specific ability to both analyze residual masses and discriminate between active disease and fibrosis/sclerosis ends up being prognostically decisive in most, if not all, cases. This concept is very important in the decision-making process, which may or may not include further treatment for patients with disease persistance after the induction phase. In addition, FDG PET could prove to be an early imaging predictive factor allowing stratifi-

cation of responding and non-responding patients after few courses of chemotherapy [25]. However, it is clear that whenever FDG PET is felt to potentially increase HD patient management quality, it should be performed at diagnosis as well, in order to allow clear-cut comparisons with those carried out at the time of restaging/follow-up.

Concerning RT, its role in advanced stage HD patients seems to be irrelevant in terms of OS and relapse-free survival (RFS), as shown by a recent European Organisation for Research and Treatment of Cancer study [26]. In this trial, a first detailed analysis showed that involved-field RT (IF-RT) did not improve RFS and OS in patients who had already achieved a CR with the MOPP/ABV regimen. Remarkably, though, those patients who had obtained a partial response (PR) and were subsequently treated with additional IF-RT had comparable overall outcome to those who had reached a CR. Once again, these data would suggest that, save for stage IA HD patients, RT might be reserved to all cases either presenting with bulky disease at diagnosis or achieving a PR following first-line CHT.

Finally, relapsing, resistant and primary progressive HD patients still pose one of the most serious challenges to the hematology/oncology scientific community [9]. According to recent data from the German Hodgkin's Lymphoma Study Group, primary progressive HD patients >50 years old, who have both a poor Karnofsky performance score and fail to attain a temporary remission on first-line treatment, have an extremely poor prognosis and should be considered for high-dose CHT (HDCT) followed by autologous stem-cell transplantation (ASCT) [27]. The same group also reports that similar conclusions should be drawn for early relapsing HD patients, particularly those who present with advanced disease and anemia at the time of relapse [28].

It is clear that, in all poor-prognosis HD patients, the only current hope for cure remains based on the possible success of HDCT followed by either ASCT [29] and/or non-myeloablative, reduced-conditioning, allogeneic SCT [16, 17]. In fact, in constrast to non-Hodgkin's lymphoma (NHL), the possible impact of novel treatment modalities including new drugs, immunotherapy and radio-immunotherapy appears not yet to be in the making.

Diffuse large B-cell lymphoma

Over the last decade, the first and foremost problem associated with the management of diffuse large B-cell lymphoma (DLBCL) has been how to move on from the shocking results of two randomized studies conducted by Fisher and colleagues. These trials proved that, for the treatment of aggressive NHL, third-generation CHT regimens were not statistically superior to CHOP [30], and that three cycles of CHOP were statistically superior to eight, provided that these three cycles of CHT were followed by IF-RT [31]. Ever since, a number of trials have been conducted either to attempt to refute these data, by also comparing standard CHOP with other treatment options, or as though these data did not exist at all, by either exploring therapeutic approaches other than CHOP or integrating CHOP with other therapeutic agents such as anti-CD20 monoclonal antibodies (R-CHOP). Regarding localized DLBCL, Fillet et al. [32] compared four cycles of CHOP with four cycles of CHOP followed by IF-RT. In that study, 455 patients were randomized to receive each treatment option, and 5-year EFS and OS were not different. The authors concluded that IF-RT following four cycles of CHOP added no benefit. Meanwhile, an update of the Southwest Oncology Group experience [31] with a follow-up in excess of 8 years now shows that PFS and OS curves have merged at 7 and 9 years, respectively [33].

As far as the combination of CHOP with passive immunotherpay is concerned, Vose et al. [34] first showed that the addition of rituximab to standard CHOP neither worsened CHT efficacy nor added any toxicity supplement to aggressive NHL patients. Even more compelling evidence in favor of this association was then provided by Coiffier et al. [35] in the elderly, in this case >60 years old, aggressive NHL patients. In particular, with a follow-up of 2 years, they found that in a randomized setting, the addition of rituximab to CHOP increased the CR rate from 63% to 76% ($P = 0.005$), the EFS from 39% to 57% ($P < 0.001$) and the OS from 57% to 70% ($P = 0.007$). Whether the further addition of rituximab alone as a maintainance treatment may exert a substantial clinical effect in this as well as in many other lymphoma settings is one of the most urgent questions that needs to be answered through randomized, controlled, phase III clinical trials.

On the other hand, and again in aggressive NHL patients >60 years old, Mainwaring et al. [36] surprisingly reported somewhat better results using a CHT regimen including mitoxantrone rather than doxorubicin. In a BNLI-sponsored, randomized trial comparing PAadriaCEBO with PMitCEBO, and with a 4-year follow-up, the latter appeared to be superior in terms of overall response (OR) rate (78% versus 69%; $P = 0.05$) and OS (50% versus 28%; $P = 0.0067$), but not in terms of CR rate and RFS.

In the substantial absence of a consensus CHT regimen accepted worldwide to treat aggressive NHL in general, and DLBCL in particular, at diagnosis, more effort appears to have been placed in possibly identifying DLBCL subtypes characterized by important prognostic differences. For instance, Wilder et al. [37] prospectively confirmed that, at diagnosis, doxorubicin-based CHT with or without IF-RT can be considered an acceptable option only for DLBCL patients with an IPI score <3. Meanwhile, Wilson et al. [38] have suggested that dose-adjusted EPOCH seems to kill DLBCL cells more effectively than a CHOP-based regimen, and this fact might prove quite important, particularly in the light of the possible identification of DLBCL subsets characterized by poorer prognosis, such as bcl-2-positive [39] and CD5-positive [40] DLBCL.

In the last few years, DLBCL has aroused a great deal of interest among researchers, becoming a model for all studies on malignant lymphomas. Its prevalence has facilitated the collection of large series of cases for the application of novel and sophisticated techniques, such as gene expression profiling and tissue microarrays. These techniques have confirmed the heterogeneity of the process, which had already been envisaged through cell morphology. However, converse to the latter, they have provided for the first time criteria for useful DLBCL subclassification, allowing the possible identification of subgroups of patients with different prognoses and different responses to the therapies already available. In addition, they have made feasible the understanding of the

molecular alterations that may be at work in each individual patient. This fact is likely to bring much closer the final goal of developing new drugs and tailored strategies capable of selectively blocking the aberrant pathways involved in the initiation, development and progression of the tumor [41].

Regarding the imaging field, PET scanning is a promising method for identifying patients that, after induction treatment, can or cannot be considered to be in CR. Thus, PET has to be considered an important technique for tailoring the specific treatment depending on the presence or absence of residual disease. In particular, most PET-positive patients at the end of the induction treatment relapse within the first 2 years [42]. In addition, early assessment with PET scan in patients with untreated aggressive NHLs may play a role in predicting the ultimate patient outcome [43].

Finally, as far as poor-prognosis, relapsed, resistant or progressive DLBCL patients are concerned, while waiting for radioimmunotherapy [44] to possibly exert a tangible role, at least for some of them, ASCT remains the favored therapeutic option of most clinicians [45, 46]. In this light, of some interest are the recent data reported by the GELA group on the better outcome of patients receiving CHT with high dose intensity prior to ASCT [47] and those reported by Vose et al. [48] on the lack of prognostic impact by the choice of either peripheral blood or bone marrow as a source for ASCT. In contrast, what seems to matter more is that either source of hematopoietic precursors could be MRD-negative by molecular analysis [48]. *In vivo* purging with rituximab therapy has been shown to be effective in follicular lymphoma patients [49], most of them showing a disappearance of bcl-2-positive cells in the harvest. However, no such marker exists in DLBCL, and the proportion of patients with circulating lymphoma cells is conspicuously lower than in indolent lymphoma. Thus, the interest in this option remains disputable, and no conclusive evidence in its favor has yet been presented.

Although there is consistent evidence for the efficacy of ASCT in patients with CHT-sensitive relapse, the role of transplantation as first-line therapy in PR or CR cases remains uncertain. In particular, previous randomized studies reported by Santini et al. [50] and Haioun et al. [47] suggested that ASCT should be restricted to intermediate-/high-risk and high-risk groups as defined by the IPI. However, we believe that such a hypothesis has to be firmly confirmed in subsequent prospective randomized trials, particularly in the light of other recent data suggesting the need for IPI age adjustment in relapsed and primary refractory DLBCL patients undergoing ASCT [51].

Finally, immunotherapy has begun to gain interest in the setting of DLBCL as well, although the very first preliminary results seem to indicate the need for complex approaches, such as that of combining adoptive transfer of co-stimulated T cells and vaccine strategies in order to possibly achieve clinical efficacy [52].

Mantle cell lymphoma

Nowadays, the only positive feature of mantle cell lymphoma (MCL) remains its relatively low epidemiological incidence [2]. As a matter of fact, from a therapeutic standpoint, most clinical trials raise only slight hopes, and not always, while no real progress has yet been made.

Possibly the most negative evidence emerging recently was reported by Howard et al. [53], who treated 40 newly diagnosed MCL patients with R-CHOP. Their findings seem to indicate that not even the tumor-specific bcl-1/IgH rearrangement disappearance according to qualitative PCR is enough to predict a better outcome in terms of PFS for the MCL patients who achieve it. However, the same concept does not seem to apply when the same modality is used as an *in vivo* purging prior to stem cell collection and ASCT [54], warranting further clinical investigation in this setting. Furthermore, since promising results have recently been observed response-wise with intensive regimens such as hyper-CVAD alone [55] or combined with rituximab [56], it is still possible that the further development of combined modality treatments of this kind may prove reasonably successful in MCL management.

Following a different approach, Lefrere et al. [57], apart from confirming the extremely poor response rate of MCL patients to CHOP alone, have shown that sequential CHT based on the administration of the DHAP regimen to all patients who do not achieve a CR with CHOP allows many more patients to proceed to HDCT in CR. However, the big problem is once again that it is still not clear at all whether HDCT followed by ASCT exerts any impact on the outcome of MCL patients. Perhaps a good way to answer this last question might be to intensify the high-dose conditioning regimen of ASCT by integrating it with a radiolabeled, anti-CD20 monoclonal antibody such as tositumomab. In this respect, the preliminary results recently reported by Gopal et al. [58] of 3-year OS of 91% and PFS of 61% justify a cautious hope.

A review from the European Blood and Marrow Transplant Registry based on the Autologous Blood and Marrow Transplant Registry for patients with MCL transplanted between 1988 and 1998 has recently been published by Vanderberghe et al. [59]. Of 340 patients identified, as many as 195 had analyzable data after record review, including 42 (21%) who had undergone ASCT in first CR. Patients transplanted in first CR had a significantly better outcome than those transplanted in any other remission status. In particular, patients transplanted in first CR featured an OS of 88% at 2 years and 65% at 5 years, as well as a PFS of 65% and 52%, respectively. Early patients, that is >60 years old, faired considerably worse than younger patients. Long-term follow-up is obviously required to both assess the impact of this treatment and to fully evaluate its curative potential [54].

Finally, standard CHT treatment followed by anti-idiotype (Id) vaccination deserves consideration as another important option for investigation in MCL. According to preliminary data, the most advanced phase II clinical trial, sponsored by the National Cancer Institute (NCI), is indeed showing encouraging and partially unexpected findings [60]. In particular, the addition of rituximab to the EPOCH regimen and the early Id vaccination following CHT completion seems to interfere only partially with the Id vaccine's capability of eliciting specific humoral responses. This fact is very important, because as it is not yet known what is the real therapeutic role played by either the humoral and/or the cellular immune response, until now it was thought that B-cell depletion caused by rituximab might hinder the overall Id vaccine effectiveness [61].

Follicular lymphoma

As nobody yet dares to envision a therapeutic strategy capable of curing an acceptable proportion of FL patients, the current state-of-the-art reflects the tendency to focus such efforts mainly towards four options: conventional CHT, HDCT followed by ASCT, allogeneic SCT and immunotherapy.

As far as conventional CHT is concerned, results remain extremely disappointing, and even the data from Lynch et al. [62] on the impact exerted by an induction combination of fludarabine and interferon-α-2a, followed by maintenance therapy with the latter, seem to confirm this overall impression.

However, not much can yet be said in favor of HDCT followed by ASCT either [63]. In particular, the data from Williams et al. [64], comparing in a case–control fashion the post-ASCT outcome of patients with *de novo* FL, transformed FL and *de novo* aggressive NHL, show no significant differences between the three groups, as well as overall results being far from satisfactory.

On the other hand, allogeneic SCT is mostly considered, as a therapeutic weapon, as intriguing, given the fact that it may possibly cure a patient, and as risky, owing to the considerable high death rate associated with it. The latter is, of course, the main reason for all such trials ending up enrolling a limited number of patients over a generally extended period of time. The study by Forrest et al. [65] is no exception to this trend. Over 8 years, as many as 24 patients with progressive FL underwent conventional conditioning and allogeneic SCT. Five early deaths were recorded, four of which were directly dependent upon the transplant procedure. Meanwhile, with a median follow-up of nearly 2.5 years, no surviving patient has yet relapsed. However, much more compelling appears to be the data from Khouri et al. [66], who with similar features in terms of both short follow-up and a small number of patients, although enrolled over a much shorter period of time, are basically reproducing the same clinical results without experiencing such a critical transplant-related mortality. Since the major difference between the two trials lies in the use of a non-myeloablative, reduced-conditioning regimen in the latter, there is no doubt that this relatively new way to manage FL therapeutically might soon prove decisive.

The field that is currently under more pressure, as far as the quest for a cure for FL is concerned, is that of immunotherapy. It is here that basic and clinical investigations seem to meet almost on a daily basis to close the gap that still exists between our knowledge and the possibility of consistently curing FL patients.

The fact that rituximab alone does not cure FL, but that it can be useful and effective in several FL patients, particularly those with low tumor burden and those for any reasons not immediately undergoing Id vaccine therapy, appears to have been established [60, 67, 68]. Moreover, very interesting results have been also reported on the capability of rituximab, sequentially added to CHOP, to greatly increase the number of previously untreated FL patients achieving a molecular response and, thereby, to improve their RFS [69]. Moreover, Czuczman et al. [70] treated 40 patients with concurrent rituximab and CHOP, achieving objective remissions in 95% of patients, including 55% CR. No unexpected toxicity was observed as an effect of the combined modality treatment, and the median time to progression was not reached after 50 months of follow-up. In contrast, it is still not possible to fully evaluate the possible impact of combined immunotherapy with rituximab and interleukin-2 for relapsed or refractory FL patients [71].

To date, the next immunotherapeutic approach in line for delivering clinical answers to clinical questions appears to be radioimmunotherapy, that is the intravenous administration of monoclonal antibodies, mainly still anti-CD20, conjugated with radionuclides such as ^{131}I (tositumomab) and ^{90}Y (ibritumomab). For the time being, probably due to a lower side-effect and toxicity intensity, the latter seems capable of outpacing the former, at least in terms of the number and type of trials being conducted and published. The bulk of evidence accumulated in favor of expanding the usage of ibritumomab in FL patients includes: (i) its safe and significant clinical activity in relapsed or refractory FL patients with mild thrombocytopenia [72]; (ii) its capability of inducing significantly better OR and CR rates than rituximab in relapsed or refractory FL patients [73]; and (iii) its effectiveness even in most rituximab-refractory FL patients [74]. On the other hand, in the absence of any comparative study between the two radiolabeled monoclonal antibodies, tositumomab has also shown substantial activity in FL patients, perhaps with a worse toxicity profile [75].

The same Id vaccine therapy that a decade ago showed, for the first time, that it was possible to immunize a cancer patient with an antigen of his own tumor [76] has now entered the arena of phase III clinical trials. Only the two such trials currently ongoing, sponsored by the NCI and Genitope, respectively, will be able to, once and for all, demonstrate whether Id vaccine clinical activity [77, 78] is correlated with better prognosis for previously untreated FL patients [79]. Meanwhile, other phase II clinical trials are also either concluded or ongoing. Among them are that sponsored by the Stanford University, on the possible improvement of the Id vaccine formulation by using Id-pulsed dendritic cells [80], and that sponsored by the University of Navarra, aiming at verifying whether Id vaccine may still be of substantial help for first-relapse FL patients [61].

Finally, despite all this great attention to treatment innovation, the search for a truly FL-suitable, independent prognostic index remains active [4, 81].

Extranodal marginal-zone B-cell lymphoma of MALT-type

The group of mucosa-associated lymphoid tissue (MALT) NHLs comprises a number of low-grade extranodal B-cell lymphomas that share similar clinical, pathological, immunological and molecular features. This condition has been widely accepted only in recent years, and has been included in the REAL/WHO classification as a specific entity, the ‘extranodal marginal-zone B-cell lymphoma of MALT-type’ (MALT lymphoma) [1, 2].

The origin of MALT lymphoma is an accumulation of autoreactive lymphoid tissue in mucosa or organs that contains no organized lymphoid tissue [82, 83]. The first required step is the recruitment of B and T lymphocytes into either the mucosa or organs that do not correspond to peripheral sites of the immune system. The acquisition of this organized lymphoid tissue, called MALT, is induced by a series of antigens, and is probably different for each organ.

This particular pathogenesis of MALT lymphoma, with a possible external (environmental or autoimmune) event as the starting point of the disease and with the preferential homing of the neoplastic cells, induces a particular behavior unique among lymphomas, which was described by Isaacson as the MALT concept [84, 85]. Regarding this concept, it is now understood that MALT lymphomas can arise synchronously or metachronously in various distinct extranodal sites, and possibly in multiple MALT and/or non-MALT sites.

Far from being rare, MALT lymphoma accounts for ~7–8% of all NHLs, being the third most frequent histological subtype after DLBCL and FL. The stomach is the most common and best-studied site of involvement [86]. MALT lymphomas have also been described in various non-gastrointestinal sites, such as salivary gland, thyroid, skin, conjuctiva, orbit, larynx, lung, breast, kidney, liver and prostate [87–101].

There are few published studies specifically reporting treatment outcome for MALT lymphoma, and even the more recent among them often refer to retrospective series of RT and CHT, with no significant difference in outcome between patients who received different initial treatments. The OS rates range between 80% and 95% at 5 years, but the PFS is significantly shorter, especially for patients presenting with advanced stage or unfavorable IPI score [102, 103].

For localized gastric MALT lymphoma, there is increasing evidence indicating that antibiotics can be effectively employed as the sole initial treatment: indeed, more than half of the treated patients achieve a histological regression of the gastric lymphoma following eradication of *Helicobacter pylori* [104]. In this context, recent advances in the knowledge of both genetic and molecular features of MALT lymphoma will probably exert a fundamental role in refining the clinical management of the disease. First and foremost, it has been shown that the presence of t(11;18) does correlate with antibiotic resistance [105, 106], progression to a more aggressive tumor and higher potential for local infiltration and distant spread [107–109].

In contrast, no treatment guidelines exist for the management of patients with non-gastric lymphoma, for those with gastric MALT lymphoma who fail antibiotic treatment or for the subset of gastric cases in which no evidence of *H. pylori* can be found. A choice can be made between conventional oncological modalities, including CHT, RT and surgery, each of them alone or in combination. However, Conconi et al. [110] recently reported interesting data on the role of rituximab in gastric MALT lymphoma; therefore, the next reasonable step for *H. pilori*-positive MALT lymphoma is the evaluation of a sequential treatment including antibiotics and rituximab, with the goal of possibly curing most patients.

Conclusion

All in all, it is increasingly evident that lymphoma treatment choice should be as case-tailored as possible, taking into account the site, the stage and both clinical and biological characteristics of the individual patient.

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