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NON-HODGKIN LYMPHOMA: HOW TO PROCEED

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Making predictions is difficult, especially concerning the future.
Historia magistra vitae.

Introduction

Less than a decade ago, one would begin such a paper stating that non-Hodgkin's lymphomas (NHL) are treated with chemotherapy, radiation and steroids and that improvements should be sought by improving cytotoxic treatment schedules and using high-dose therapy and auto- or alografting in an appropriate manner. However, the last few years have witnessed a revolution in the treatment of non-Hodgkin's lymphomas (NHL) that resulted from the use of a different class of drugs, namely monoclonal antibodies. In the meantime, smart drugs, proteasome inhibitors, immunomodulators, histone deacetylase (HDAC) inhibitors and antiangiogenic drugs are being tested and in some instances approved for the treatment of other types of cancers. On the other hand, improvements in understanding lymphoma biology have enabled us to realize that all NHLs are not created equal and that different prognostic groups can be identified even within single histological subtypes. All these new drugs and concepts have created a shifty field with a lot of possibilities making predictions of future treatment approaches very difficult.

Monoclonal antibodies

The introduction of rituximab, a humanized murine monoclonal antibody directed against the CD20 antigen, has led to an improvement of outcomes of patients with B-cell NHL unparalleled since the invention of CHOP chemotherapy more than 30 years ago (1). The addition of rituximab to standard chemotherapy has improved all outcomes studied, including overall survival, in practically every phase III trial performed, be it first-line or salvage treatment, indolent or aggressive NHL etc. All this has been achieved without

increasing treatment-related toxicity, making this success even more fascinating. Indeed, rituximab seems to be a lucky jack-pot winner and in retrospective it is hard to imagine a better designed monoclonal antibody. The CD20 antigen is present in all developmental stages of B-cells from late lymphoblasts to preplasmocytes. Therefore, rituximab is active against all B-NHL types but spares hematopoietic progenitors and immunoglobulin-secreting cells, thus resulting in low toxicity. CD20 antigen is not internalized nor shed, thus an antibody binding to it will remain on the cell surface for a prolonged period of time. Also, there will be no loss of antibodies due to binding to soluble parts of the antigen. The Fc portion of the antibody activates type 1 immunologic reactions. Presumably, these immunologic reactions are important for the activity of the drug but, surprisingly, this has not been proven yet (2).

The success of rituximab has led to a flood of me-too antibodies, either directed against different antigens or against CD20 but with some presumed improvement. However, their success is by no means guaranteed. One should keep in mind that rituximab was not the first antibody used for treatment of lymphomas. This title belongs to alemtuzumab, directed against CD52 (1,3). After a cautious start, alemtuzumab was almost abandoned because of toxicity, until improvements in infection prophylaxis and a more ambitious industrial sponsor made it resurface in the treatment of CLL. CD52 is present also on T-cells and treatment with alemtuzumab results in T-cell depletion, mimicking AIDS. It is therefore not surprising that lessons from the AIDS epidemic have taught us infection prophylaxis methods necessary for safe administration of alemtuzumab. While the drug is registered for treatment of fludarabin-refractory CLL, unfortunately after more than a decade no randomized trials have been performed to prove its efficacy in T-cell NHL.

Radioimmunotherapeutic agents are monoclonal antibodies conjugated with radioactive isotopes (4). Their antitumor activity is thought to result from the combination of immunologic mechanisms triggered by antibody binding to the cell surface and effects of radiation that are not limited to the bound cells but also affect neighboring „bystander“ cells. Currently two drugs are registered, ibritumomab and tositumomab, both directed against the CD20 antigen. In contrast to rituximab, these drugs result in prolonged myelosuppression. Currently, it seems that the best bet for radioimmunotherapy in NHL is to use it as a consolidation treatment after induction with immunochemotherapy or for conditioning prior to transplantation. Studies, designed to explore these possibilities, are underway.

Smart drugs and cytotoxic agents

The proteasome inhibitor bortezomib and immunomodulators (or as some would claim, antiangiogenic agents) thalidomide and presumably lenalidomide are active in mantle-cell NHL (MCL) (5,6). They are being explored also in other types of lymphomas, most notably, diffuse large B-cell (DLBCL) and follicular lymphoma. HDAC inhibitors seem to be active in cutaneous T-cell NHL (CTCL) (7) and antiangiogenic drugs, such as bevacizumab, show some activity in aggressive NHL (8). Enzastaurin, a protein-kinase C (PKC) inhibitor, is being tested for remission maintenance in DLBCL.

This abundance of „smart“ drugs has resulted in a shift away from testing new and improving combinations of classic cytotoxic agents that might not be completely appropriate. A rare example to the contrary is gemcitabine whose activity in hematological neoplasia has been long disregarded, but new studies confirm its activity in Hodgkin's lymphoma and NHL, especially CTCL of the peripheral T-cell type (PTCL) (9).

Indolent B-NHLs

Indolent NHLs have a slow course and respond favorably to treatment but, unless localized, invariably relapse. Therefore, it is customary not to treat patients until they become symptomatic. Most patients with indolent NHL finally die of their disease but a significant proportion dies of unrelated diseases, 15% of them never needing lymphoma treatment. Rituximab is active as monotherapy, in combination with cytotoxic agents, in induction and remission maintenance, however only very few patients, if any, are cured with this approach. The biggest problem is not to achieve remission, but to prevent relapse. Therefore radioimmunotherapy consolidation after remission induction with immunochemotherapy, with or without autografting, seems a plausible option for achieving the holy grail of indolent NHL treatment, namely cure of disseminated disease. Trials are being planned to test this hypothesis. Whether immunomodulating agents or proteasome inhibitors will play a role in maintenance or, less probably, induction treatment remains to be seen.

DLBCL

The addition of rituximab to CHOP resulted in 10-20% improved cure rates, still about 40% of patients, most with high-risk features, die of their disease. Approximately half of the failures are due to refractoriness and half to relapses. Most relapses occur within a relatively

short period of two years, indicating that, in contrast to indolent NHL, DLBCL cells are unable to survive long without proliferating. Currently it is everybody's guess whether the solution of the DLBCL problem lies with new cytotoxic agents, different combinations of standard cytotoxic agents (e.g. dose-adjusted EPOCH), radioimmunotherapy, PKC inhibitors, immunomodulators etc. but the author of this paper does not believe that it lies in shortening the interval between CHOP cycles from three to two weeks (10). Current data suggest that DLBCLs can be divided in at least two groups, those with gene expression profiles similar to germinal center B-cells (GC-type) and those similar to activated B-cells (ABC) (11). The latter have a worse prognosis. Future genetic studies might enable us to understand molecular changes leading to DLBCL development and design smart drugs that will interfere with these processes, in a way similar to the effect of imatinib in Ph+ CML.

MCL

MCL has a bad prognosis, with less than 30% of patients surviving 5 years. This is due to its refractoriness to treatment (similar to DLBCL), propensity for relapsing (similar to indolent NHL) and the fact that it most frequently affects elderly patients unable to tolerate intensive chemotherapy. It seems that, at least in younger patients, an old cytotoxic agent, namely cytarabine, might improve the outcome, especially when combined with rituximab and autografting (12). Radioimmunotherapy might prove to be useful in patients with molecular, but probably not hematological, relapses. While the prospects for elderly are less bright, bortezomib, thalidomide and, presumably, lenalidomide containing combinations currently seem to be the best bet (4,5).

PTCL

PTCLs also have a bad prognosis, with less than 30% of patients surviving 5 years. They do not express CD20 and have therefore largely remained untouched by improvements of the last decade. Intergroup randomized trials are being planned to test the value of alemtuzumab added to CHOP for induction treatment. However, for the purposes of prediction, one should not forget a few facts. First, the variability between PTCLs is even larger than between DLBCLs. Currently, we are not able to define real disease entities within this group and that, as well as their relative rarity in the developed world, hinders future improvements. Advances in biology might shed new light at PTCLs in a way that we are

today unable to foresee. Second, the role of anthracyclines is less certain in PTCL than in B-NHLs (13). If doxorubicin is not a very effective cytotoxic agent, new combinations, e.g. gemcitabine + cisplatin or high-dose methotrexate + l-asparaginase might be better than CHOP. Regarding new drugs, HDAC inhibitors are being explored in PTCLs (8). Angiommunoblastic lymphoma might be an attractive target for antiangiogenic drugs (but also for cyclosporine) (14,15). This is clearly a field where new approaches and better intergroup collaboration is needed.

Burkitt's lymphoma (BL)

Let us end this paper on a brighter note. New data, coming from German researchers, suggests that BL should not be a problem in younger patients anymore, of course provided the diagnosis can be made and treatment started in time to prevent development of severe tumor-lysis syndrome (16). The combination of rituximab and high-dose methotrexate based intensive chemotherapy results in cure rates up to 90%. Unfortunately, patients older than 50 do not tolerate this type of treatment and their results are therefore inferior. Whether, like in osteosarcoma, different combinations of cytotoxic agents with equivalent activity and reduced toxicity can be found, remains to be seen. While relapsing or refractory BL is generally regarded as a lost cause, very preliminary data suggest that topotecan, a cytotoxic agent used for treatment of solid cancers, in combination with doxorubicin might show surprising activity (17).

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