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Aurer, Igor

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CHANGING THERAPEUTIC LANDSCAPE – THE LAST DECADE

Igor Aurer

Division of Hematology, Department of Internal Medicine, University Hospital Center Zagreb and Medical School, University of Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia; tel: +385-1-2388-265, fax: +385-1-2421-892, e-mail: aurer@mef.hr

Running title: Changing Therapeutic Landscape

ABSTRACT

Undoubtedly the most important event in the previous decade in lymphoma treatment was the establishment of immunotherapy as a prime modality. Addition of rituximab improves survival in almost every group of patients with CD20+ tumors. This has led to the appearance of a number of “me too” monoclonal antibodies (MoAbs) as well as MoAbs directed against other antigens whose usefulness remains to be proven during the next decade. We have also seen the raise and, probably unwarranted, fall of radioimmunotherapy. Conventional radiotherapy is losing ground.

Regarding chemotherapy, the success of attempts to supplant R-CHOP-21 for front-line treatment of DLBCL with more dose-dense or dose-intense regimens remains doubtful and this issue is still unresolved. Bendamustine appeared as possibly the most effective cytotoxic agent for treatment of indolent lymphomas, while treatment of HL is becoming more tailored to prognostic features. This decade has also seen the advent of targeted drugs for lymphoma treatment. Their real impact will become known in the years to come.

Finally, we may hope that advances in understanding the biology of lymphomas, made in the last decade, will help resolve remaining critical issues, treatment of T-NHLs and high-risk DLBCLs, being probably the most prominent.

INTRODUCTION

For every physician interested in lymphomas (lymphomaniacs as some might call us) treatment of lymphomas is a fascinating topic. The variability in lymphoma types, clinical presentation and host biology make multiple therapeutic modalities and strategies possible. And while significant treatment changes in previous years were few and hotly debated, the last decade has seen a fundamental shift in the therapeutic landscape, at least for B-NHLs. This was caused by the widespread use of rituximab, a monoclonal antibody directed against the CD20 B-cell antigen. Other new agents also appeared or are appearing: various monoclonal antibodies conjugated or unconjugated; targeted drugs; new (or old but previously not well known) cytotoxic drugs. Results of some pivotal clinical trials have also impacted profoundly on everyday treatment of lymphomas in this decade. In this paper I will review the changes in lymphoma treatment that have occurred during the previous decade and briefly allude to those that might happen in the next few years.

RITUXIMAB

Rituximab, a chimeric unconjugated monoclonal antibody (MoAb) directed against the CD20 antigen, present at all stages of B-cell development except for early lymphoblasts and plasma-cells, has been registered for treatment of relapsing / refractory indolent B-NHLs in the late nineties and for the front-line treatment of aggressive and indolent B-NHLs in the beginning of this millennium [1]. The use of this drug has increased dramatically during this decade, and it is now considered one of the most important, if not the most important drug, for treatment of B-NHLs. There are two main reasons for this. The first is that rituximab dramatically improves outcomes of patients, not only disease-free survival (or similar endpoints like event-free survival, freedom from treatment failure, etc) but also overall survival. The addition of rituximab to standard chemotherapy improves survival of patients with diffuse large B-cell lymphoma (DLBCL) by 10-20%, an improvement that was previously achieved only by anthracyclines in the seventies [2-4]. This effect is not limited to clinical trials but has been substantiated in community-based epidemiological studies [5]. And while the difference in survival in patients with indolent lymphomas seems at first glance less impressive (around 2.5% per year), one should keep in mind that no other drug or therapeutic procedure has ever been consistently shown to improve survival in this patient population [6-10]. The second reason for rituximab popularity is that its toxicity is almost negligible, apart

from occasional infusional and allergic reactions, a slight increase in granulocytopenia that is of doubtful clinical significance and the propensity to cause hypogammaglobulinemia in patients receiving prolonged maintenance treatment.

Currently, the most important unanswered question is not which patients with CD20+ NHLs should receive rituximab but which patients should not, i.e. what is the proper definition of refractoriness to rituximab. The most frequently used definition of refractoriness is progression within six months from the last rituximab dose but I am hard pressed to believe that it doesn't matter whether a patient fails rituximab monotherapy maintenance (one dose every three months) or a dose-dense or dose-intense combination of rituximab and polychemotherapy.

It is intriguing to note that, despite the importance and widespread use of rituximab, neither the exact mechanism of action of the drug, nor the physiologic role of CD20, have been completely elucidated [11]. While this does not impact so much on rituximab itself, it might throw some doubt on the ability of bioengineers to improve immunotherapy by manipulating complement-binding or effector cell-binding characteristics of monoclonal antibodies.

RADIOIMMUNOTHERAPY

Two radioimmunodrugs have caused a lot of excitement in the last decade. Both consist of a MoAb directed against CD20 and a radioactive isotope. Ibritumomab-tiuxetan conjugated to radioactive yttrium is more popular in Europe, while tositumomab conjugated to radioactive iodine is more frequently used in North America [12,13]. In contrast to the latter, the former is a pure beta emitter, can be administered without prior in-vivo dosimetry and the dose of radioactivity excreted by the patient is almost negligible. All these characteristics make the outpatient use of ibritumomab-tiuxetan possible. This seems to be illegal in the USA, which explains the difference in popularity of these drugs on opposite sides of the Atlantic. In contrast to rituximab, radioimmunotherapy causes significant hematological toxicity and can therefore be either used as monotherapy or combined with chemotherapy in a transplant setting.

Both drugs are registered for treatment of follicular lymphoma (FL), an indication which in the opinion of the author is suboptimal. There are many other treatments available for this indication and the pharmaceutical companies marketing these drugs might serve patients with NHL and themselves better if they continue to support clinical trials exploring

the ability of these drugs to consolidate responses in high-risk patients with aggressive or advanced B-NHLs.

ALEMTUZUMAB

We now know how to reduce the toxicity of alemtuzumab, the oldest MoAb around, but this anti-CD52 MoAb is still toxic, causing significant immunosuppression due to its T-cell depleting activity. The frequent and sometimes severe infusional reactions can be significantly reduced by administering the drug subcutaneously instead of intravenously [14]. Its possible role in treatment of T-NHL remains unproven but randomized trials comparing chemotherapy regimens with and without the addition of alemtuzumab are underway, so hopefully we will have the answer in this decade.

BENDAMUSTINE

Strictly speaking, bendamustine is not a new drug. This cytotoxic agent, which combines the characteristics of alkylating agents and antimetabolites, was synthesized in the sixties in former East Germany [15]. The drug was therefore developed behind the iron curtain in a rather unsystematical way and very few foreign physicians where aware of it prior to the unification of Germany. Since then, bendamustine has emerged as a very exciting "new" cytotoxic agent for treatment of lymphomas. Randomized trials, mostly from Germany, suggest that it is the most effective cytotoxic drug for treatment of indolent lymphomas with a very acceptable toxicity profile, generally limited to myelosuppression, provided the dosage is reduced to 90 mg/m^2 over 2 days every 3 weeks.

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Addition of rituximab to chemotherapy is unquestionably the standard of care for up-front treatment of DLBCL. However, when it comes to the choice of chemotherapy regimens, in the last decade we took a step back or as the French might put it "on plus ca change, on plus c'est le meme chose". Rituximab (R) seems to act as an equalizer reducing the benefits of more intensive chemotherapy [3]. Even the Germans have given up very intensive treatment approaches like Mega-CHOEP [16] and a recently presented French study suggest that there is no difference between R-CHOP given every 2 weeks (R-CHOP14) and CHOP given every

3 weeks (R-CHOP21) [17]. So CHOP21 is still standing as a reasonable treatment option for newly diagnosed patients in the greatest part of the world, together with CHOP14 and CHOEP in west and north Europe, ACVBP in France and French speaking parts of Belgium and infusional dose-adjusted EPOCH at the NCI and some North American cooperative groups.

Something similar happened with salvage regimens. A Dutch trial proved that the addition of rituximab to salvage chemotherapy prior to autografting improves response and survival, at least in patients that had not received it up-front [18]. When it comes to the choice of chemotherapy regimens, the only major randomized trial in this setting ended up in a draw. Outcomes of relapsing or refractory DLBCL patients treated with R-DHAP and R-ICE are the same [19]. So everyone will still stick to his/her favorite salvage regimen!

The role of radiotherapy seems to be diminishing. First, the French showed that even patients with stage 1 disease can be safely treated without irradiation and then the Germans showed that after the end of immunochemotherapy it is not necessary to irradiate areas of previously bulky disease that are in complete remission [20,21].

The support for autografting in first remission is diminishing except in countries where this approach is traditionally very popular, like Italy and France, and in high-risk patients, in whom an American trial will hopefully finally prove or disprove the usefulness of this approach. In the salvage setting autografting is still standing tall. Preliminary results suggest radioimmunotherapy might play a role in consolidating remissions in patients with high risk of relapse after abbreviated up-front therapy [22]. It seems plausible to extend these data to salvage setting and patients who are not candidates for autografting, mostly because of age. Allografting is slowly gaining ground, with ever more patients failing other approaches being referred to this, still rather drastic, treatment method [23]. However, the exact place and importance of allografting in treatment of DLBCL patients as well as the up and down sides of reduced intensity conditioning remain to be discerned in the decades to come.

MANTLE-CELL LYMPHOMA (MCL)

Changes of the therapeutic landscape in MCL in the last decade took two directions. First, the role of autografting in first remission after rituximab-containing chemotherapy was established by large trials [24]. Second, new drugs, the immunomodulators, thalidomide and lenalidomide, the proteasome inhibitor bortezomib and the mTOR inhibitor temsirolimus have improved the bleak outlook of failing patients [25-28]. Remission rates with these drugs are

around 50%, while remissions last sometimes longer than those achieved with previous therapy. Interestingly, the first three drugs are used to treat myeloma, a neoplasia sharing cytogenetic and molecular abnormalities with MCL.

These improvements have resulted in an increase in survival rates of 50% and above at five years [24]! Opposite from what one would have guessed earlier, the superiority of high-dose cytarabine containing regimens over standard R-CHOP has not been established yet, results of a large European trial designed to prove this are still unknown.

PERIPHERAL T-CELL LYMPHOMAS (PTCL)

I believe that, in contrast to B-NHL, the biggest improvement in T-NHL that the last decade has witnessed is the new WHO classification [29]. The ability to properly differentiate between PTCL types will help design targeted treatments and improve outcomes of these, frequently fatal, disorders. Other topics worth mentioning include results of phase II studies of up-front aggressive chemotherapy and autografting in patients with systemic PTCL [30,31], data suggesting that asparaginase is very active against NK-lymphomas [32] and the additions of pralatrexate and histone-deacetylase inhibitors vorinostat and romidepsin to the list of possible treatment modalities for PTCL and cutaneous T-cell lymphomas respectively [33-35]. Unfortunately, response rates to these novel agents are around a meager 30%. So far best results obtained in patients with PTCL using chemotherapy followed by autografting come from a large Nordic study using CHOEP for remission induction [31]. They report survival rates of 50% at 5 years suggesting that etoposide might be an important drug for the treatment of PTCL-NOS and ALK- ALCL.

BURKITT'S LYMPHOMA (BL)

The combination of rituximab with high-dose methotrexate containing regimens results in survival rates above 80%, albeit with significant toxicity [36]. But there seems to be a way to overcome this problem. The NCI group has shown that at least similar, if not better results, can be achieved using the infusional dose-adjusted R-EPOCH regimen [37]. If their results are corroborated, BL might become the most curable of all lymphoma types!

INDOLENT LYMPHOMAS

Rituximab has become a standard drug for treatment of indolent lymphomas in almost every setting. It can be given for remission induction alone or in combination with chemotherapy, for response maintenance, up-front or in salvage settings. In contrast, the choice of up-front chemotherapy is still largely determined by tradition with Great Britain, Scandinavia and Netherlands favoring CVP, Germany and middle Europe CHOP, France even more aggressive regimens as CHVPP, etc. However, this discussion might soon be obsolete because one recently reported randomized trial showed that rituximab and bendamustine is superior to R-CHOP both in terms of response and toxicity [38]. Thus, this drug might easily become the cytotoxic of choice for up-front treatment of indolent lymphomas.

The biggest problem with indolent lymphomas is generally not how to induce remission but how to prevent relapse. Interferon, which was used before, has significant side-effects and its efficacy is debatable. Rituximab, in contrast, is the perfect drug for this purpose. Randomized trials have shown that it improves remission duration in all patients and survival in those that have not received rituximab in combination with chemotherapy for remission induction [39,40]. The survival improvement ranged between 8% (from 77% to 85%) and 20% (from 57% to 77%) at 3 years. Thus, maintenance treatment of patients with indolent nodal B-NHL is rapidly becoming the standard of care.

The use of rituximab has made possible to obtain complete remissions more frequently and of a better quality (i.e. with less minimal residual disease) than before [41]. This probably translates in better outcomes of autografting for patients with follicular lymphoma and possible other nodal indolent lymphoma types. This resulted in an increase in the use of this procedure for remission consolidation.

Improvements in both induction and maintenance treatment of indolent lymphomas have negatively affected the popularity of radioimmunotherapy. Studies designed to register these drugs for earlier disease phases generally did not use what are now considered best available treatment options, making conclusions on the usefulness of radioimmunotherapy for treatment of newly diagnosed patients or those in first relapse or second remission difficult [13,42].

Extranodal marginal zone lymphomas (MALTomas) seem to be a very special lymphoma type. The fact that gastric MALTomas can be cured with antibiotics alone is not so new, but now it seems that the same is true for MALTomas of ocular adnexa [43]. And even patients who fail this approach almost never die of their lymphoma [44]. General acceptance of these facts has led to a reduction in the use of cytotoxic drugs for these type of lymphomas.

CEREBRAL LYMPHOMAS

The last decade has witnessed the widespread recognition that cerebral NHLs are not a very rare and invariably fatal disorder treatable (but not curable) only with radiotherapy. High-dose methotrexate is now firmly established as the treatment of choice of these disorders, high-dose cytarabine seems to be catching on, especially for high-risk patients [45]. This is probably the only B-NHL type where rituximab does not seem to play a major role. In contrast, consolidative radiotherapy still seems to be very important. These changes resulted in improvements in survival that is now around 30% and even more for younger patients with less initial neurologic deficits.

HODGKIN'S LYMPHOMA (HL)

Two substantial changes occurred in treatment of HL in the last decade. The first is the widespread acceptance of evidence-based up-front treatment tailored towards prognostic factors. For very favorable patients a reduction in number of treatment cycles and radiation dose is warranted, while for unfavorable patients, ever more physicians, at least in Europe, accept escalated BEACOPP as the standard of care [46,47]. The second is the introduction of gemcitabine as a very active drug for treatment of HL patients failing standard up-front and salvage treatments [48].

It should be remembered that omitting radiotherapy in localized HL is not supported by evidence [49] and that, despite the fact that PET is frequently used for interim response evaluation, its usefulness in this setting remains unproven.

CONCLUSIONS

The last decade has seen a paradigm shift in treatment of lymphomas, from ever more aggressive chemotherapy and transplantation approaches towards more targeted and risk-adapted treatment. The MoAb rituximab has become one of the best selling drugs ever, markedly changing the outcome of patients with B-NHL but also the attitude of physicians and pharmaceutic companies towards cancer treatment. While at times this went so far as to make any further support for development of cytotoxic drugs difficult to obtain, bendamustine reinvigorated the interest in cytotoxic drugs. Currently a number of different monoclonal

antibodies and targeted drugs are being explored for the treatment of lymphomas, with histone-deacetylase inhibitors, immunomodulators and mTOR and proteasome inhibitors already used in clinical practice. This diversity of drug types will increase in the future with ever more drugs affecting different pathways important for lymphoma development to follow.

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