Overview

One and a half decades of the Lugano International Conference on Malignant Lymphoma: Variations on a theme or true progress?

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It has been 15 years since the First International Conference on Malignant Lymphoma convened in Lugano. Five hundred sixty registrants attended that first meeting, where 61 papers were presented, along with 48 posters, selected from 350 abstracts. By the sixth conference, the number of presented papers had grown to 110, out of 750 submitted abstracts, and almost 2000 participants were in attendance.

This brief introduction summarizes a few of the highlights of the Sixth Lymphoma Conference and places them in the context of the many achievements and advances in the understanding and treatment of lymphoma over the past decade and a half. In this way, we may better understand both the importance of what has been learned and see more clearly the directions in which these developments are taking us.

The first conference, held in 1981, was organized by Cavalli and others. The first four papers were presented by DeVita, Kaplan, Berard, and Bonadonna. The last paper on opening night was delivered by Gianni Bonadonna on the evolution of treatment strategies for malignant lymphomas, a topic that Bonadonna has pursued diligently and for which he was honored during the fifth conference with the San Salvatore Foundation Award when he delivered the 1993 Kaplan Memorial Lecture.

During that first conference, various histopathological classifications were discussed extensively. Immunological markers were introduced for routine use, and the Kiel classification found wide acceptance in Europe. Berard gave a preview of the International Working Formulation (IWF). Subsequently, the IWF gained wide clinical use, at least in the United States, for its easy translation of the histopathological findings into clinical entities. By 1994, with the emergence of new entities and more immunological, cytogenetic, and molecular characterization, it was time for a revision, as had become clear from issues raised at the fifth conference the preceding year. Harris and coworkers soon introduced the REAL classification, a detailed histological and immunological system, which leaves room for modification and recognition of yet-to-be identified subgroups.

The clinical applicability of the REAL classification and identification of prognostic groups has been reviewed extensively.

This new classification appears to be able to group the different lymphomatous diseases into clinically relevant entities, but it will have to be ascertained if it is reproducible on a large scale outside university centers. It offers us the opportunity to categorize lymphomas according to modern immunologic and molecular biologic criteria and allows us to view each subgroup as a discrete entity. Together with the International Prognostic Index, and perhaps the other biologic markers reviewed by Shipp at the most recent conference, the REAL classification may enable prognosis within subtypes.

One of the new entities identified in recent years and now classified in the REAL classification is the group of MALT lymphomas. At the sixth conference, one complete session was devoted to these lymphomas. At the preceding conference, in 1993, Wotherspoon had reported regression of gastric MALT lymphomas after eradication of Helicobacter pylori. Indeed, over 90% of low-grade MALT lymphomas in the West are associated with H. pylori. The same year, Cavalli presented the intriguing results of a multicenter study in Italy and southern Switzerland in treating MALTOMAS with amoxicillin, metronidazole, and omeprazole. This treatment has been shown to eradicate over 60% of these lymphomas. Isaacson and Wright had paved the way for this remarkable discovery ten years previously when they described the MALT lymphoma concept. These successes underscore the importance of careful correlative studies that put together clinical and pathologic observations.

During the second lymphoma conference in 1984, Riggs and Muggia pointed out in their talks a relationship between AIDS and NHL. Longo gave a paper on AIDS, and Gallo emphasized the role of viruses in lymphoma. Virology has remained an important theme since then, with a multitude of papers on HTLV-1 and HIV at the third conference in 1987. The role of EBV in Hodgkin's disease would be a key issue at the 1990 conference, as highlighted in the introductory lecture by Broder. During the fifth conference in 1993, the pathogenesis of EBV in certain lymphomas was shown by Kieff, Stein, and Diehl, who suggested an important role for the incorporated EBV genome. This work was updated during the 1996 conference by Kieff, who proposed a model for regulation of B-cell growth by LMP-1.
Knecht and colleagues were able to demonstrate that the same mutations and base pair deletions may occur in specific regions of the EBV latent membrane protein oncogene in both Hodgkin's disease and nasopharyngeal carcinoma.

The mechanisms of viral transformation were further elucidated during the 1996 conference. Data were presented on how transgenic mice overexpressing the EBV-encoded BHRF1 gene are prone to develop lymphomas. Hints have emerged of successful therapy with immune modulators in post-transplant lymphoproliferative disorders, which are commonly EBV related. Liebowitz and O'Reilly discussed, respectively, interferon-α and immune cytotoxic T cells in this regard. Knowles reported on the HIV and Kaposi's sarcoma-associated herpesvirus in body cavity-based lymphomas. The rising incidence of HIV and increased numbers of immunosuppressed patients will make it a certainty that these topics will be debated in future conferences.

In 1987, Rowley gave an elegant keynote lecture on specific chromosome aberrations in non-Hodgkin's lymphoma and lymphocytic leukemia. The recognition of these chromosomal changes led to the identification of specific genes involved in lymphomagenesis. The story of cytogenetics and oncogenes merged in the presentation by Croce entitled 'Molecular Genetics of B-cell Neoplasia' at the fourth conference in 1990. Many other papers on bel-2 in follicular lymphoma and the prognostic significance of chromosome abnormalities were presented at that conference. This discussion culminated in 1993, when major attention was given to the developing area of molecular genetics and cytogénetics, in particular, to the oncogene bel-2 and apoptosis. Dalla-Favera gave an overview of current research in this area. Persistent bel-2 was shown to have prognostic significance for recurrence of follicular lymphoma after bone marrow reinfusion. Better understanding of this and many other molecular markers now enables better diagnosis and prognostication of our patients. A more targeted treatment should lead to improved outcome.

In his keynote address at the sixth conference, Korsmeyer outlined the role of bel-2, bax, bad, and other family members in apoptosis. In particular, he showed how this family and their complex dimerizations determine whether a cell will die or survive or, after a second hit, such as c-myc dysregulation, become a malignant lymphoma. Today, tumor-suppressor genes and proto-oncogenes remain at the forefront of research, and at the 1996 conference, papers were given on p53, bel-1, bel-3, and bel-6. It is known that the bel-1 locus on chromosome 11 is involved in up to 75% of mantle-cell lymphomas, thus supporting its position in the REAL classification as a discrete biological entity. Bel-6 may predict an improved survival in follicular lymphoma. In post-transplant lymphoproliferative disorders, bel-6 mutations may predict nonresponders to simple withdrawal of immunosuppression as the only therapy.

By the next conference, in 1999, some of these molecular markers will probably be part of routine histopathological staging and follow-up of patients. Treatment may be selected according to chromosomal aberrations and molecular mutations. And more important, such oncogenes may themselves become targets for therapy. Work from the Royal Marsden Hospital has already shown minor responses using antisense nucleotides to bel-2 in patients with relapsed NHL.

Encouraging basic scientific work was presented at the 1996 conference, allowing better understanding of the biology of malignant cells. Wolf and colleagues presented their successful establishment of a Reed-Sternberg cell line from peripheral blood mononuclear cells. Pinto and coworkers described how the eosinophil in Hodgkin's disease may have a pathogenic role by way of its CD30 ligand. In his keynote lecture, Rajewsky showed that the majority of Reed-Sternberg cells have immunoglobulin gene rearrangements and are clonal. This suggests that Reed-Sternberg cells arise from germinal center cells and perhaps postgerminal center cells.

Since 1984, with the advent of monoclonal antibodies, the concept of the so-called magic bullet has been eagerly discussed. In 1987, Köhler gave the Henry Kaplan Memorial Lecture 'Monoclonal Antibodies: Current Status and Research.' Some of the theoretical considerations presented were already being used in clinical research at that time. In general, these approaches attempt to exploit immunological differences between malignant and host cells. At the 1996 conference, at least three different antibodies directed against 'the tumor cell' were discussed: Grillo-Lopez reported on the use of a yttrium-90-labeled anti-CD20. In a phase I trial in relapsed lymphoma, he achieved 4/17 CRs. McLaughlin and others used anti-CD20 by itself in relapsed follicular and low-grade lymphoma. With PCR, the bel-2 oncogene could not be detected in peripheral blood and bone marrow of some patients previously positive for bel-2. Hartmann used the bispecific antibody anti-CD30/CD16 in Hodgkin's disease with 2 responders out of 15 patients treated. And Foss and colleagues used the IL-2 receptor on T cells as a target in cutaneous T-cell lymphomas by coupling DAB389, a diphtheria toxin to IL-2, and saw a 37% response rate. Obviously, this field is in its early stages, and better targeting and the avoidance of host responses to the therapeutic antibody will be challenges for the future. In coming lymphoma conferences, there are sure to be further reports on the success of this approach.

Another promising area of applied immunotherapy includes idiootype vaccination against surface immunoglobulins of lymphoma cells. Investigators at Stanford have vaccinated a number of patients after completion of their chemotherapy and found a prolonged freedom from progression and a trend toward better overall survival compared to historical controls.

In the clinical arena, many of the old topics continue to be debated. The controversy of the best treatment regimen for NHL was discussed by Fisher and Gianni at the most recent conference. Outside clinical trials, CHOP remains the standard for treatment of intermediate- and possibly of high-grade lymphomas. However, the new
REAL classification might be able to detect subgroups of patients with a better or an inferior prognosis, who may benefit from a less or more aggressive treatment approach, respectively. Armitage has shown in his retrospective reclassification of 1400 patients according to the REAL classification, for example, that Ki-1-positive anaplastic large-cell lymphomas may carry a better prognosis. These differences may in part explain why, 20 years after the introduction of CHOP, none of the newer and more intensive combination regimens has been able to demonstrate a superior survival. However, Gianni's data using high-dose sequential, single-agent chemotherapy at each drug's MTD rather than classic combination regimens is intriguing and needs to be investigated in a randomized trial. Over the years it has become evident that, whatever the treatment modality for aggressive lymphomas, the drugs should be administered at a maximum dose intensity. This approach includes the larger group of elderly patients, who comprise over 30% of all NHLs. The GELA reported on their results of treating 450 patients of 69 years and older with full-dose, curative-intent chemotherapy. Both toxicity and overall survival are comparable to those of younger patients.

High-dose chemotherapy with autologous bone marrow rescue and, more recently, peripheral blood progenitor cell reinfusion have been studied for the past decade. A clear advantage has been shown for early therapy in first remission for patients with poor prognosis. For patients in first relapse, the Parma study showed a significant improvement in event-free and overall survival with high-dose chemotherapy (BEAC) versus salvage chemotherapy with DHAP. In contrast, Gieselbrecht presented data from a randomized trial showing inferior results with early high-dose chemotherapy compared to standard chemotherapy. In an earlier randomized trial from the GELA for patients in CR, consolidation with high-dose chemotherapy improved survival in high and high-intermediate risk patients. A randomized trial from the SWOG showed provocative results with only three cycles of CHOP chemotherapy followed by involved-field radiation versus eight cycles of CHOP alone in patients with stage I and II aggressive NHL. The future may lie in short but intensive chemotherapy regimens followed by radiation to the areas of prior bulk disease.

Several investigators from Europe, the United Kingdom, and Canada treating Hodgkin's disease with combined modality chemotherapy and radiation therapy have come to similar conclusions. Thus, the debate from the early 1980s continues as to whether and how chemotherapy and radiation therapy should be combined. However, over the last decade radiation techniques have improved, with smaller and better-delineated radiation fields.

Much has been accomplished over the last fifteen years. The advent of multiagent chemotherapy in the treatment of lymphoid malignancies has resulted in curative therapeutic interventions. The Henry Kaplan Memorial Lecture by Saul Rosenberg, for example, permitted a view through his eyes of the remarkable progress in the treatment of Hodgkin's disease. Obstacles and pitfalls remain: particularly the toxicity of therapy. While better supportive care, including colony stimulating factors and antibiotics, allows us to handle most acute situations, long-term toxicity remains a challenge. Hoppe reviewed this topic during the 1996 conference. The recently published SEER data on incidence and mortality of Hodgkin's disease bear out nationally the successes reported by Rosenberg. In males, white as well as black, the incidence of Hodgkin's disease is falling steadily, and mortality has dropped remarkably.

These successes, with achievement of long-term cures, have now revealed the long-term toxicities of the treatment protocols. At 15 years, 20 years, and later, the deaths from complications - including second cancers, cardiovascular events, and late infections - exceed the deaths from recurrence of Hodgkin's disease by far. Changes of the treatment protocols, as reported during the most recent conference, may reduce complications and thus optimize the ratio of cure rates and toxicity.

The SEER data for NHL are much less encouraging: in fact an 'epidemic' of NHL is anticipated. The increased incidence of NHL and increased mortality can only in part be explained by the ever-growing AIDS epidemic. Nevertheless, and offering a glimmer of hope, the five-year survival rate in patients with NHL has increased from 30% in the 1970s to 52% in the early 1990s.

As regards low-grade follicular lymphoma: In 1984, Lister reported on his findings of the usefulness of interferon-α in low-grade non-Hodgkin's lymphoma, and has since then presented regular updates. Although only a few therapeutic results were presented at the 1996 conference, new drugs like 2-CDA and fludarabine had been introduced in previous years, yielding high response rates and suggesting a prolonged time to progression. While disease control with these newer regimens may be sufficient for elderly patients, a curative treatment approach for younger patients suffering from follicular lymphoma is still lacking.

The Sixth International Conference on Malignant Lymphoma summarized the great developments and progress in understanding the pathogenesis and treatment of lymphoma. It also marked the beginning of a new era, with introduction of more targeted and immunologically based therapy into the clinic. Great progress has been made with combination chemotherapy, but with standard treatments we have reached a plateau. Randomized trials of high-dose chemotherapy with peripheral blood progenitor cell support and new intensive sequential treatment regimens are underway or planned. Incorporation of new treatment concepts and immunological modulation may lead to further improvements. When translating the great progress of molecular biology into the clinic, the importance of controlled trials cannot be overemphasized. Some lymphoma subtypes, such as as MALTOMA, EBV-associated lymphoproliferative disorders, and Hodgkin's disease, may be treated in a completely different manner when the seventh conference convenes in 1999.