Multiple Myeloma: Oncogenomics for Targeting Tumor Cells in the Microenvironment

Speaker: Kenneth Anderson, Dana-Farber Cancer Institute, Boston, Massachusetts

Recent progress in the research on multiple myeloma (MM) demonstrates the tumor-promoting influence of the microenvironment. Growth factors promote tumor cell proliferation and survival, and cytokines and chemotactic factors promote tumor cell migration and invasion. Proteases break down the basement membrane, alter the architecture of tissue structures, and promote migration and invasion by tumor cells. The vasculature of tumor cells is composed of endothelial cells that are uniquely altered in different tumors. Tumors produce growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which recruit endothelial cells, thus affecting the growth of the tumor vasculature.

Gene modulation (up-regulation) occurs after the binding of MM cells to bone marrow stem cells, causing an increase in tumor growth potential and the release of adhesion molecules, cytokines, and proteasomes that affect the microenvironment. When myeloma sets up residence in the bone marrow, the myeloma cells activate cytokines, promoting drug resistance as well as molecules that affix tumor cells to receptor sites, making them almost impossible to eradicate with conventional treatments.

Some emerging drugs, however, appear to be able to overcome intrinsic drug resistance, inhibit angiogenesis (blood vessel growth), prevent tumor cells from adhering to bone marrow, and augment the patient’s own immune defenses by increasing the number of circulating natural killer T cells.

Lenalidomide. Lenalidomide (Revlimid®, Celgene) is an oral thalidomide analogue that targets both tumor cells and their microenvironment. Early clinical trials indicate that it overcomes conventional drug-resistance mechanisms in a few patients with relapsed or refractory MM. In a phase 3 trial of 700 patients, there was a significant increase in response rates, in disease-free periods, and in time to disease progression in the lenalidomide/dexamethasone treatment arm, compared with the dexamethasone (control) arm. After 20 months, rates of clinical remission were 20% with lenalidomide/dexamethasone and 4% with dexamethasone; rates of partial remission were 60% with lenalidomide/dexamethasone and 22% with dexamethasone.

A New Drug Application for lenalidomide/dexamethasone for the treatment of MM is near approval.

Bortezomib. Bortezomib (Velcade®, Millennium), a proteasome inhibitor, targets MM cells in the bone marrow microenvironment and milieu. Proteasome inhibitors are a new class of targeted therapies that may be more effective in patients with relapsed or refractory blood cell cancers such as MM. They block MM cells to the stroma and inhibit angiogenesis.

The drug received accelerated approval for the treatment of relapsed refractory MM. The initial therapy for MM patients may eventually include combinations of bortezomib/thalidomide/dexamethasone, lenalidomide/dexamethasone, bortezomib/lenalidomide, or bortezomib alone. Bortezomib/doxorubicin combinations showed activity in patients with advanced MM.

IKB Kinase (IKK) and SCIO-469. Novel therapies targeting the bone marrow microenvironment include IKK inhibitors and the p38 mitogen-activated protein (MAP) kinase inhibitor SCIO-469, which blocks interleukin-6 (IL-6) and VEGF secretion from bone marrow stem cells. An ongoing clinical study is being conducted to determine whether SCIO-469 will have a positive impact on the microenvironment in patients with MM.

NPI-0052. NPI-0052 is an oral proteasome inhibitor that kills all three bortezomib-resistant cells (beta 1, beta 2, and beta 5). Clinical trials are expected to be under way soon.

Vatalanib. PTK 787 (vatalanib), a tyrosine kinase inhibitor, prevents VEGF-induced effects in MM cells and in bone marrow. It is indicated for angiogenesis, to inhibit the maturation of dendritic cells, and to increase bone-resorbing activity.

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**Meeting Highlights: ASH Symposium, Myeloma and Lymphoma**

**Telomestatin.** Telomerase is found in the nucleus of MM cells and is overexpressed in MM. Telomestatin, an intramolecular G-quadruplex intercalating drug with specificity for telomeric sequences, will be studied in MM patients.

**Deacetylase.** The histone deacetylase (HDAC) inhibitor of cell signaling HDAC6 (tubacin), one of 11 known human HDACs, may have therapeutic value in treating MM. Aside from deacetylating tubulin, HDAC6 has a fascinating function; it binds both polyubiquinated proteins (those marked for degradation by attached ubiquitin “flags”) and dynein (a protein motor associated with microtubules), bringing the two together to help the cell “clean house.” This takes place through a cell structure called the aggresome. Studies of tubacin, in combination with bortezomib, are under way.

**Initial Therapy and Therapeutic Sequencing in Multiple Myeloma**

**Speaker:** Paul Richardson, Dana-Farber Cancer Institute, Boston, Massachusetts

**Lenalidomide/Dexamethasone.** The combination of lenalidomide and dexamethasone is effective for newly diagnosed MM. It demonstrated a 91% overall objective response with a complete response in 6% of the patients. An ongoing study of lenalidomide and dexamethasone (at a lower dose) is in progress to establish better tolerability than that found in the previous standard dosing study. Results to date indicate that lenalidomide/dexamethasone provides high anti-cancer responses when it is used as an initial therapy.

A phase 3 study of lenalidomide 25 mg/day plus dexamethasone 40 mg/day versus dexamethasone plus placebo was conducted in the U.S., Canada, Europe, Israel, and Australia. The primary endpoints were time to tumor progression (TTP), overall survival, myeloma response rate, and safety. The combination therapy showed a high rate of response and clinical remission and a TTP of 15 months, versus five months with dexamethasone plus placebo.

Common adverse drug events (ADEs) included neutropenia, thrombocytopenia, anemia, and deep vein thrombosis (DVT) or pulmonary embolism. It was concluded that lenalidomide 25 mg plus high-dose dexamethasone significantly prolonged the TTP ($P < .0001$). The combination was well tolerated with predictable and manageable side effects.

**Bortezomib versus Dexamethasone.** Bortezomib, a small-molecule boronic acid dipeptide reversible proteasome inhibitor, prevents interactions of MM cells with bone marrow stromal cells and the secretion of cytokines, including IL-6, VEGF, and insulin growth factor-1 (IGF-1). In a large phase 3 study, Assessment of Proteasome Inhibition for Extending Remissions (APEX), bortezomib demonstrated superior efficacy to high-dose dexamethasone in relapsed MM. There was a significant TTP benefit ($P < .0001$), with a 78% increase in the median TTP. There was also a response rate advantage ($P < .0001$) (38% vs. 18%), clinical remission, and partial remission, and clinical remission plus partial remission with bortezomib (13%) versus dexamethasone (2%).

**Bortezomib/Lenalidomide.** In a combination study of bortezomib/lenalidomide in MM patients, the beneficial effects were found to be additive and synergistic. The bortezomib dose was 1–1.3 mg/m$^2$ IV. The oral dose of lenalidomide was 5–10 mg each day. The remission rate (clinical + partial + minimal) was 91%. There were no discontinuations or serious ADEs through the first three cohorts. The results were encouraging, and another 10 patients will be enrolled at the maximum tolerated dose. Future investigations will include phase 2 trials of relapsed and refractory MM and newly diagnosed MM.

**Thalidomide/Dexamethasone.** Several clinical studies have compared the thalidomide/dexamethasone combination with dexamethasone alone in MM patients. Superior response rates were found with the combination in newly diagnosed MM, but the combination was associated with higher toxicity than dexamethasone alone. There was also a need for DVT prophylaxis with the drug combination. The higher response rates of thalidomide/dexamethasone must be weighed against increased toxicity for individual patients.

**Stem-Cell Transplantation in Myeloma**

**Speaker:** Thomas Shea, University of North Carolina School of Medicine, Chapel Hill, North Carolina

**Melphalan.** High-dose chemotherapy appears to be commonly used to treat MM. Researchers compared the two most widely used conditioning regimens in a prospective, randomized trial before autologous stem-cell transplantation in patients with newly diagnosed symptomatic MM. The patients were younger than 65 years old. Those in arm A received 8 gray (Gy) of total-body irradiation (TBI) plus 140 mg/m$^2$ of melphalan; those in arm B received 200 mg/m$^2$ of melphalan (Alkeran®). A total of 282 evaluable patients were compared.

The results showed that melphalan 200 mg/m$^2$ was less toxic and at least as effective a conditioning regimen as 8 Gy of TBI with melphalan 140 mg/m$^2$. This regimen should be considered the standard of care before autologous stem-cell transplantation in MM.

A randomized trial of high-dose chemotherapy with melphalan 140 mg/m$^2$ plus TBI, followed by either one or two successive autologous stem-cell transplantsations, was conducted. A complete or very good partial response was achieved by 42% of patients in the single-transplant group and by 50% of patients in the double-transplant group.

The investigators concluded that double transplantation improved overall survival among MM patients, compared with single autologous stem-cell transplantation, after high-dose chemotherapy, especially in patients who did not have a very good partial response after undergoing a single transplantation.

**Autologous and Allogeneic Transplantation.** The use of autologous versus allogeneic transplantation is an important consideration in MM. A study was conducted to compare the results of autologous and allogeneic peripheral hematopoietic stem-cell transplantation (HSCT) in 87 patients with MM using a myeloablative preparative regimen. Autologous transplantation ($n = 70$) led to a lower 100-day procedure-related mortality (4%) than did allogeneic transplantation (18%) ($P = .02$).

Complete responses were seen more often in allogeneic recipients (64%) than in autologous recipients (34%) ($P = .09$). For the autologous recipients, survival at one year was 86% but fell to 50% at four years. For the allogeneic recipients, survival at one and at four years remained at 64%. Thus, for patients who...
survived more than one year, the four-year survival rate was superior in the allogeneic recipients (100%) than in the autologous recipients (58%) \((P = .02)\).

A trend toward higher relapse was seen with autologous transplantation (73%) than with allogeneic transplantation (37%) \((P = .1)\). Although autologous HSCT is associated with a lower rate of transplantation-related mortality, allogeneic HSCT has an accepted mortality rate and is more likely to provide a sustained response. Allogeneic HSCT may be suitable in younger patients, soon after diagnosis, and in those with chemotherapy-sensitive disease.

**Follicular, Large-Cell, and Mantle-Cell Lymphoma: Overall Biology and Pathology**

**Speaker:** Randy D. Gascoyne, British Columbia Cancer Agency, Vancouver, British Columbia

_Follicular lymphoma_ is the most common subtype of non-Hodgkin's lymphoma (NHL) in North America. _Diffuse, large B-cell lymphoma_ is the most common lymphoma subtype. It comprises at least two diseases: germinal center B cell–like (GCB) disease and non-germinal center activated B cell–like (ABC) disease. Genomic imbalances have an independent predictive value and add to the molecular predictor. _Mantle-cell lymphoma_ represents about 6% of all NHLs and comprises small B-cell lymphoma with aggressive, relentless clinical behavior. The proliferation signature represents an integrator of oncogenic events.

Mantle-cell lymphomas are remarkably consistent in their phenotype. They are typically CD5-positive, CD10-negative, CD23-negative B-cell NHLs that strongly express surface immunoglobulin D (IgD) or M (IgM), predominantly of the gamma light-chain type.

Mantle-cell lymphoma is associated with a recurring cytogenetic abnormality, t(11;14)(q13;q32), that involves the bcl-1/PRAD-1 gene. This abnormality results in the overexpression of cyclin D1 protein. Although cyclin D1–positive lymphomas other than mantle-cell lymphoma have been encountered, several studies indicate that the overexpression of the PRAD-1/cyclin D1 gene is a highly specific marker of mantle-cell lymphoma. Microarray studies have revealed the differential expression of several genes in mantle-cell lymphoma, but it is unknown which of these differences are dependent on the transformed mantle cell itself or on the tumor microenvironment.

We need more knowledge to understand the biology of mantle-cell lymphoma to improve therapy. Genome-wide analysis tools should provide additional insights.

**Therapy for Follicular Lymphoma**

**Speaker:** David G. Maloney, Fred Hutchinson Cancer Research Center, Seattle, Washington

Follicular lymphoma represents 22% of new NHL diagnoses. The most common forms are indolent or low-grade. There is a progressive transformation of the follicular center B cell. The human bcl-2 gene is an oncogene candidate, which is involved in the t(14:18) translocation specifically associated with follicular and diffuse B-cell lymphomas.

**Rituximab.** Rituximab (Rituxan®, Genentech/Biogen Idec) has changed the treatment paradigm of patients with B-cell lymphomas. This monoclonal antibody is considered the first effective targeted therapy approved by the U.S. Food and Drug Administration (FDA) for the treatment of lymphoproliferative disorders. Despite its efficacy and safety profile, sustained complete remissions have been documented in a relatively small proportion of patients treated with rituximab monotherapy.

To improve antitumor activity, initial strategies combined rituximab with standard chemotherapy drugs; this approach led to higher response rates; improved disease-free survival; and, in some cases (i.e., with diffuse large B-cell lymphoma), prolonged overall survival. Although rituximab has been incorporated into multiple chemotherapy regimens, such as CVP (cyclophosphamide, vincristine, prednisone), CHOP (cyclophosphamide, hydroxydaunomycin, Oncovin® [vincristine], prednisone), and FND (fludarabine, mitoxantrone, dexamethasone), many lymphoma patients either experience relapse after an initial response or do not respond because of either intrinsic or acquired resistance.

Scientific efforts are being focused toward developing new strategies to improve rituximab activity. A review of past, ongoing, and future research with a diverse group of exciting novel agents follows next.

**E1496 Trial.** E1496 was a phase 3 trial of CVP chemotherapy with or without maintenance therapy with rituximab. Intermediate-risk patients with follicular lymphoma receiving CVP plus rituximab maintenance therapy had a one-year overall survival rate of 89% and a two-year progression-free survival rate of 70%. The patients received four cycles every six months for two years. Thus, there is a benefit of adding rituximab sequentially after chemotherapy. Rituximab delays the TTP in the intermediate-risk and high-risk groups of patients.

**Rituximab–CHOP Trial.** A phase 3 study of rituximab–CHOP (R-CHOP) as a first-line therapy for follicular lymphoma demonstrated a favorable median time-to-treatment failure in 68 months versus 21 months with CHOP alone. The median progression-free survival rates were 50 months with R-CHOP and 15 months with CHOP.

**M39023 Trial.** The M39023 study utilized MCP (mitoxantrone, chlorambucil, prednisolone) chemotherapy for six cycles every four weeks and rituximab–MCP (R-MCP) for six cycles every four weeks. This was followed by restaging; one group of patients received MCP for two cycles every four weeks, and R–MCP was given to patients with stage III/IV follicular lymphoma for two cycles every four weeks. The median ages were 62 and 61 years, respectively.

Remission rates for the intent-to-treat population and clinical remission rates for the R–MCP patients and those with follicular lymphoma who received MCP were 92.4% and 75%, respectively \((P < .0001)\), and 49.5% and 25%, respectively \((P < .0001)\). Progression-free survival was significantly prolonged with R-MCP (88.5% at 19.7 months; the median was not reached), compared with MCP (55% at 19.7 months).

This study confirms the recently published data of rituximab plus chemotherapy in the first-line treatment of indolent NHL. R–MCP may become the new standard, especially for elderly patients with follicular lymphoma.

**Iodine 131–Tositumomab Trial.** 131I-Tositumomab (anti-
Management of Relapsed, Refractory Follicular Lymphoma

Speaker: Stephanie A. Gregory, Rush University Medical Center, Chicago, Illinois

Clinical trials in patients with relapsed follicular lymphoma have shown that rituximab plus CHOP therapy (R-CHOP) is better than CHOP therapy alone. Rituximab maintenance therapy following initial FCM (fludarabine, cyclophosphamide, mitoxantrone) chemotherapy, with or without rituximab, resulted in a 94% overall response (P<.011). There was a trend toward improved overall survival following rituximab maintenance therapy after three years.

Radioimmunotherapy using ibritumomab tiuxetan (linked to the indium 111 radioisotope) in these patients demonstrated long-term positive responses (overall response, 85%). ^131^I-Tositumomab in patients with refractory disease produced a durable (event-free) responder rate of 30% up to eight years.

In another study, which compared ^131^I-tositumomab with chemotherapy, the overall response rate was greater with ^131^I-tositumomab than with chemotherapy after seven encounters. Clinical responses after treatment resulted in 40% responders with ^131^I-tositumomab after many remissions and after several lines of therapy.

Thus, radioimmunotherapy yields higher overall response and clinical remission rates when integrated earlier in the treatment sequence for relapsed follicular lymphoma. There is a high incidence of durable responses, especially in patients who achieved clinical responses. Radioimmunotherapy with ^131^I-tositumomab or ibritumomab tiuxetan should be given early consideration for patients with relapsed, low-grade follicular or transformed NHL.

The potential for long-term, disease-free survival for patients with recurrent follicular lymphoma who receive high-dose chemotherapy and an autologous HSCT is unknown. A retrospective study was conducted in 248 patients with recurrent follicular lymphoma who received high-dose chemotherapy and autologous HSCT. The median follow-up of surviving patients was six years (range, 1–16 years). Disease progressed in 117 patients (47%); 80 patients subsequently died, and as of this writing, 37 have survived after disease progression.

The study showed that long-term event-free survival is possible following high-dose chemotherapy and autologous HSCT for follicular lymphoma.

Myeloablative single-agent ^131^I-tositumomab and autologous HSCT phase 1 and 2 trials are ongoing. Allogeneic HSCT in relapsed follicular lymphoma, as seen in the Seattle study, utilized a nonmyeloablative regimen in matched related donors and unrelated donors. After three years, in the matched-related donor group of patients, rates were 80% for overall survival and 60% for event-free survival; in the unrelated donor patients, the rate of overall survival and event-free survival was about 60%.

In the MD Anderson Cancer Center transplant study, nonmyeloablative transplantation—rituximab, initially followed by fludarabine/cyclophosphamide, followed by rituximab 1,000 mg/m^2^ once daily—showed an overall survival rate of approximately 90% at 50 months after transplantation.

The following therapeutic agents are being studied in clinical trials of follicular lymphoma:

- galiximab + rituximab
- bortezomib + rituximab
- denileukin diftitox (Ontak™, Seragen) + rituximab
- favid vaccine (made from a patient’s biopsy tumor specimen)
- oblimersen sodium (Genasense®, Genta) + rituximab
- bendamustine (Treanda™, Salmedix) + rituximab
- bendamustine + mitoxantrone (Novantrone®, Serono) + rituximab
- epothilones

Treatment of Early-Stage and Late-Stage Diffuse, Large B-Cell Lymphoma

Speaker: Richard I. Fisher, University of Rochester Medical Center, Rochester, New York

Rituximab plus CHOP (R-CHOP) is the standard initial therapy for all patients with advanced-stage, diffuse, large B-cell lymphoma. This standard was obtained following a randomized clinical study that compared CHOP chemotherapy plus rituximab with CHOP alone in elderly patients with diffuse, large B-cell lymphoma.

The rate of complete responses was higher in the patients who received R-CHOP (76%) than in those receiving CHOP alone (63%) (P<.005). With a median follow-up of two years, event-free and overall survival times were significantly higher in the R–CHOP group (P<.001 and P<.007, respectively). Adding rituximab to standard CHOP chemotherapy markedly reduced the risk of treatment failure and death. Clinically relevant toxicity was not significantly greater with R–CHOP.

Thus, the addition of rituximab to the CHOP regimen increases the complete response rate and prolongs event-free and overall survival in elderly patients with diffuse, large B-cell lymphoma, without a clinically significant increase in toxicity. A four-year update of this study shows that these survival rates were better with R–CHOP than with standard CHOP.

Treatment of aggressive lymphomas includes new therapeutic approaches, including monoclonal antibodies plus chemotherapy, dose intensification using cytokines, modifiers of drug resistance, ablative chemotherapy with bone marrow or peripheral blood stem-cell support, and new chemotherapeutic agents. One new approach is CHOP therapy every two weeks instead of the standard 21 weeks. CHOP every two weeks improved overall survival in patients older than 60 years of age. A study of rituximab plus dose-accelerated CHOP is ongoing.

A number of studies of new and older agents for the treatment of aggressive lymphomas are under way. A few Southwest Oncology Group (SWOG) trials are in progress.
• SWOG 0349 is utilizing CHOP, rituximab, and G3139 phosphorothioate oligonucleotide (bcl-2 antisense) therapy for patients younger than 60 years of age with advanced-stage diffuse, large B-cell lymphoma and NHL of low and low–intermediate risk.

• SWOG 0515, phase 2, is evaluating CHOP and rituximab plus bevacizumab for patients older than 60 years of age with advanced-stage diffuse, large B-cell lymphoma and NHL. The objective is to determine the complete response rate and the two-year failure-free survival. R–CHOP plus bevacizumab is used for eight cycles.

• SWOG-0433, phase 2, is under way to assess 131I-tositumomab in combination with CHOP and rituximab for patients older than 60 years of age with advanced-stage diffuse, large B-cell lymphoma and for NHL patients.

Chemo-radiation therapy is standard treatment for localized aggressive lymphoma. To determine the optimal therapy for non-elderly persons with low-risk localized lymphoma, a randomized trial comparing chemotherapy with chemotherapy alone was conducted. After five years, chemotherapy with three cycles of ACVBP (doxorubicin [Adriamycin®], cyclophosphamide, vindesine, bleomycin, prednisone), followed by sequential consolidation, was superior to three cycles of CHOP plus radiotherapy for the treatment of low-risk localized lymphoma in patients under 61 years of age. Radiotherapy should have an impact on early-stage disease.

Relapsed and Refractory Diffuse, Large B-Cell Lymphoma

Speaker: Thomas C. Shea, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Salvage therapy for relapse of diffuse, large B-cell lymphoma depends on the answers to several questions:

- Which relapse is it?
- Which therapies have been used in the past?
- What was the last interval of response?
- Was the prior response complete or partial?
- What are the patient’s characteristics and profile (age, organ function, medical history, and comorbidities?)

A study was conducted to determine the response rate and toxicity of GDP (gemcitabine, dexamethasone, cisplatin [Platinol®]) chemotherapy for recurrent or refractory NHL. The primary endpoint was a complete or partial response after two cycles and followed by HSCT.

GDP was an active regimen in patients with large B-cell lymphoma along with acceptable toxicity to outpatients. In patients with recurrent or relapsed NHL, the response rates (progression-free and overall survival) with R-ICE (rituximab, ifosfamide, carboplatin, etoposide) chemotherapy was greater than with ICE chemotherapy alone.

Initial therapy dictates the outcome in elderly patients with diffuse, large B-cell lymphoma. The outcome of 94 consecutive elderly patients treated for aggressive lymphoma without a low-grade component showed that the median survival was 26 months and the five-year overall survival was 39% (range, 27%–50%). Twenty patients had disease that was refractory to first-line CHOP or CHOP-like therapy, and only one of 20 patients was alive with active lymphoma. This study suggests that conventional-dose, second-line chemotherapy yielded disappointing results for these elderly patients.

A randomized trial of high-dose therapy plus autologous stem-cell support with the standard regimen of CHOP was conducted. The patients, aged 15 to 60 years, had untreated aggressive lymphoma with a low, a low–intermediate, or high–intermediate risk of death (i.e., with a maximum of two adverse prognostic factors), according to the age-adjusted International Prognostic Index.

The primary outcome was event-free survival at five years. High-dose chemotherapy with autologous stem-cell support was superior to CHOP in adults with disseminated aggressive lymphoma. However, rituximab was not used in this study.

The results of high-dose chemotherapy and autologous HSCT (autotransplantation) in patients with diffuse aggressive NHL who had not achieved a complete response with conventional chemotherapy were of interest. Seventy-nine (44%) of 184 patients achieved complete response or a complete response with residual imaging abnormalities of unknown significance after autotransplantation.

Thirty-four (19%) of 184 patients achieved partial responses, and 55 (31%) of these patients had no response or progressive disease.

The researchers concluded that high-dose chemotherapy and autologous HSCT should be considered for patients with diffuse, aggressive NHL who do not achieve a complete response but who are still chemotherapy-sensitive and who would otherwise be appropriate candidates for transplantation.

In summary, salvage therapy for diffuse, large B-cell lymphoma suggests that patients may benefit from the addition of antibody therapy for less than three months before HSCT.

Therapies for Mantle-Cell Lymphoma

Speaker: Michael E. Williams, University of Virginia School of Medicine, Charlottesville, Virginia

The key concerns in treating mantle-cell lymphoma are the need to understand (1) the biological and prognostic subtypes, (2) the best initial therapy, (3) the best treatment options for relapsed disease, (4) the role and timing of HSCT, and (5) emerging therapies.

No one initial therapy has proved superior, although several combinations have been partially successful. The combination of rituximab plus CHOP (R–CHOP) has been fairly successful, with a 96% overall response rate and a 48% rate of complete remission. CHOP, CVP, fludarabine, chlorphosphamide, F-IDA (fludarabine, idarubicine), and PEP-C (prednisone, etoposide, procarbazine, cyclophosphamide) have also been used. Response durations usually last for eight months to a year.

A randomized trial was conducted to compare the combination of R–CHOP with CHOP alone as first-line therapy for advanced-stage mantle-cell lymphoma. One hundred twenty-two previously untreated patients were assigned to six cycles of CHOP (n = 60) or R-CHO (n = 62). Patients up to 65 years of age who achieved a partial or complete remission underwent a second randomization to either myeloablative radio-

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chemotherapy, followed by autologous HSCT, or interferon- 
alpha (IFN-α) maintenance therapy. All patients older than 
65 years of age received IFN-α maintenance therapy. R-CHOP 
was significantly superior to CHOP in terms of overall 
response rate (94% vs. 75%) (P = .0054), complete remission 
rate (34% vs. 7%; P = .00024), and time to treatment failure 
(median, 21 vs. 14 months) (P = .0131). No differences were 
observed in progression-free survival.

In conclusion, combined immunochemotherapy with 
R-CHOP brought about a significantly higher response rate and 
a prolonged time to treatment failure, compared with chemother- 
apy alone. Hence, R-CHOP may serve as a new baseline 
regimen for advanced mantle-cell lymphoma, but further 
 improvement is needed in terms of novel strategies that 
can be used during remission.

**Rituximab plus Hyper-CVAD.** A prospective phase 2 trial 
was conducted to determine the response, failure-free sur- 
vival, and overall survival rates and toxicity of rituximab plus 
an intense chemotherapeutic regimen in patients with previously 
untreated aggressive mantle-cell lymphoma. Patients received 
rituximab plus fractionated hyper-CVAD (cyclophosphamide, 
vincristine, doxorubicin [Adriamycin®], dexamethasone) 
(considered one cycle), alternating every 21 days with ritux- 
imab plus high-dose methotrexate-cytarabine (considered one 
cycle) for a total of six to eight cycles.

Of 97 assessable patients, 97% responded; 87% achieved a 
complete remission or unconfirmed complete remissions. 
With a median follow-up time of 40 months, the three-year fail- 
ure-free rate was 64%, and the overall survival rate was 82%, 
without a plateau in the curves.

It was concluded that rituximab plus hyper-CVAD, alter- 
nating with rituximab plus high-dose methotrexate and cytar- 
abine, was effective in untreated, aggressive mantle-cell lymph- 
oma. Toxicity was significant but expected.

**Rituximab plus FCM.** In a prospective, randomized study 
in patients with relapsed mantle-cell lymphoma, rituximab 
improved the prognosis when it was combined with 
chemotherapy. A total of 147 patients received four courses of 
chemotherapy with fludarabine 25 mg/m² on days one to 
three, cyclophosphamide 200 mg/m² on days one to three, and 
mitoxantrone 8 mg/m² on day one (FCM), alone or combined 
with rituximab 575 mg/m² (R-FCM). The R-FCM arm experi- 
enced better progression-free survival (P = .0381) and overall 
survival (P = .003).

In patients with follicular lymphoma, progression-free sur- 
vival was significantly longer in the R-FCM arm (P = .0139). In 
patients with mantle-cell lymphoma, a significantly longer 
overall survival time was observed with R-FCM (P = .0042). 
There were no differences in clinically relevant ADEs in either 
study arm. Hence, the addition of rituximab to FCM chemother- 
apy significantly improved the outcome of relapsed or 
 refractory mantle-cell lymphoma.

**Bortezomib.** In four studies of relapsed mantle-cell lymph- 
oma, bortezomib showed 40% to 50% efficacy in response 
rates over a period of months to two years. In one study, when 
rituximab was given for four weeks, followed by thalidomide, 
all patients required dose reductions, from 400 mg, during 
maintenance. The overall response rate for 18 patients was 83%.

**Temsirolimus.** As an inhibitor of the mammalian target of 
rapamycin (mTOR), temsirolimus is under study for relapsed, 
refractory mantle-cell lymphoma. Table 1 presents additional 
novel therapies being studied for mantle-cell lymphoma.

### Table 1: Therapies for Mantle-Cell Lymphoma

<table>
<thead>
<tr>
<th>Target</th>
<th>Approach</th>
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<tbody>
<tr>
<td>bcl-2</td>
<td>Antisense, rituximab</td>
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<tr>
<td>Cyclin D1</td>
<td>Flavopiridol, mTOR inhibitor</td>
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<td>Immunoglobulin idiotype</td>
<td>Tumor vaccine; allo-HSCT or mini-allo-HSCT</td>
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<td>Proteasome</td>
<td>Bortezomib</td>
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<tr>
<td>Angiogenesis/microenvironment</td>
<td>Thalidomide, lenalidomide</td>
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HSCT = hematopoietic stem-cell transplantation; mTOR = mammalian target of rapamycin.

#### Hodgkin’s Lymphoma

**Speaker:** Joseph M. Connors, British Columbia Cancer Agency, Vancouver, British Columbia

**ABVD Chemotherapy.** The gold standard of treatment for Hodgkin’s lymphoma includes four cycles of ABVD (doxo- 
rubicin, [Adriamycin®] bleomycin, vinblastine, dacarbazine) 
for stage IA, IIA low-bulk tumors and six to eight cycles for 
bulky tumors. For the 80% of patients with advanced disease 
but without a large number of adverse prognostic factors, 
standard multiagent chemotherapy with the well-established 
ABVD regimen provides the best balance of effectiveness and 
minimization of toxicity. More intensified regimens currently 
under investigation are appropriate for the 20% of patients with 
numerous adverse prognostic factors.

**BEACOPP Chemotherapy.** A BEACOPP regimen (bleo- 
mycin, etoposide, doxorubicin [Adriamycin®], cyclophos- 
phamide, vincristine [Oncovin®], procarbazine, prednisone) 
was developed to investigate the potential of moderate-dose 
escalation of conventional polychemotherapy to improve the 
unsatisfactory treatment results in advanced-stage disease. 
Following pilot studies, the randomized trial demonstrated 
that BEACOPP, at the baseline dose, attained superior failure-
free survival to COPP/ABVD and that a dose escalation 
brought about a further marked improvement. Toxicity was 
severe but manageable. The BEACOPP regimen is highly 
effective, and moderate-dose escalation results in a further 
worthwhile improvement in tumor control.

#### Summary

The prognosis for elderly patients with advanced 
disease, in contrast to that of younger patients, has not im-
proved substantially over the last 20 years. The most effective 
method of therapy for refractory or relapsed Hodgkin’s lymphoma is still unresolved in terms of whether to use high-
dose or conventional aggressive chemotherapy. High-dose 
chemotherapy, followed by autologous HSCT (BEAM [etopo-
side, cytarabine, melphalan]–HSCT), is frequently used to 
treat patients with relapsed disease and may be the best strat-
agy. Today, it is not enough to focus solely on a cure for this 
disease; the treatment program must maximize the chance of 
cure and minimize late-stage toxicity.