Cure the Incurable: Immunochemotherapy for Follicular Lymphoma

February 18, 2013

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Follicular lymphoma is an indolent, or slow-growing, lymphoma of follicular B cells, and is the second most common form of non-Hodgkin's lymphoma. At the time of diagnosis, 85% of patients with FL have widespread disease and are considered incurable by conventional therapies. Over the last 15 years, treatment approaches using various combinations of chemotherapy and immunotherapy have drastically improved patient survival. However, there is no consensus on the best frontline treatment regimen. Immunotherapy uses monoclonal antibodies directed against the cell surface protein CD20 that is found on both normal and malignant B cells. Antibody binding to CD20 activates the immune system to attack and kill the cancerous B cells, and makes these cells more susceptible to chemotherapy. Attaching a radioactive isotope to the antibody allows targeted delivery of radiation to the cancerous cell. To compare the efficacy of two different anti-CD20 antibodies, a phase III trial randomized FL patients using a frontline chemotherapy regimen with either unlabeled rituximab or Iodine-131 (^{131}I) radiolabeled-tositumomab was carried out and found the two regimens equally efficacious.

Drs. Oliver Press, Ajay Gopal, and David Maloney of the Clinical Research Division and Dr. Michael LeBlanc and Joseph Unger of the Public Health Sciences Division contributed to this Southwest Oncology Group (SWOG) and Cancer and Leukemia Group B phase III trial (SWOG S0016). Previous sequential phase II studies examined various frontline FL treatment regimens; the current study is an extension of protocol SWOG S9911. Between March 1, 2001 and September 15, 2008, 554 patients with previously untreated, advanced FL were enrolled. All patients received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) every 21 days for six cycles. The arm with CHOP alone was closed in December 15, 2002 with only 17 patients after trial results from another study demonstrated that the addition of rituximab markedly improved both progression-free survival and overall survival. The remaining patients were randomized to either CHOP plus six doses of rituximab administered during and after chemotherapy (CHOP-R, n=267), or CHOP followed by consolidation tositumomab/^{131}I-tositumomab therapy after 4-8 weeks (CHOP-RIT, n=265).

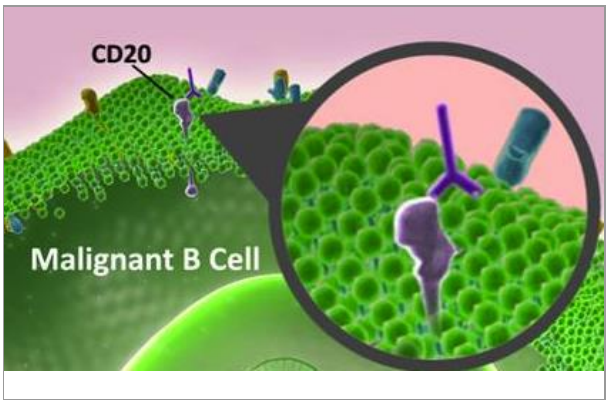
Rituximab leads to B cell death through a variety of mechanisms, including antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis of CD20-positive cells. ^{131}I-

tositumomab has the added benefit of targeted delivery of radiation to CD20-positive cells to further eliminate cancerous cells disseminated throughout the body. The two-year and five-year estimates of progression-free survival were equally good for the CHOP-R and CHOP-RIT arms (76% *versus* 80%, *P*=0.11; 60%*versus* 66%, *P*=0.05) after a median follow-up of 4.9 years. The two-year and five-year estimates of overall survival were also equivalent for the two treatment arms, 97% and 92% on CHOP-R and 93% and 86% on CHOP-RIT (*P*=0.08).

The side effects and toxicities were similar for both CHOP-R and CHOP-RIT, and included mostly hematologic events typical of CHOP therapy. CHOP-R patients had more severe febrile neutropenia, or fevers (16% *versus* 10%, *P*<0.05), as found in previous studies. More thrombocytopenia was observed with RIT (18% *versus* 2%, *P*<0.0001), as was hypothyroidism (7% *versus* 3%,*P*<0.07) and HAMA (human anti-murine antibody) formation (17% *versus* 2%, *P*<0.06), as expected with RIT although it did not reach significance. Secondary malignancies are a major concern with the radiolabeled antibodies; however, the incidence of secondary malignancies was similar for CHOP-R and CHOP-RIT at the last follow-up point (9% *versus* 8%).

While both therapies treat frontline FL with a similar level of efficacy, a combined strategy of CHOP-R followed by RIT could be superior and warrants future trials. Importantly, follow-up of the phase II CHOP-RIT trial (SWOG S9911) currently has a 10-year progression-free survival rate of 60%, and findings suggest that immunochemotherapy may prevent the relapse of disease and cure a subset of advanced stage FL patients previously thought to be incurable.

Press O.W., Unger J.M., Rimsza L.M., Friedberg J.W., Leblanc M., Czuczman M.S., Kaminski M., Braziel R.M., Spier C., Gopal A.K., Maloney D.G., Cheson B.D., Dakhil S.R., Miller T.P., and Fisher R.I. 2013. Phase III Randomized Intergroup Trial of CHOP Plus Rituximab Compared With CHOP Chemotherapy Plus ^{131}Iodine-Tositumomab for Previously Untreated Follicular Non-Hodgkin Lymphoma: SWOG S0016. *Journal of Clinical Oncology*. 31:314-20



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Rituximab and Iodine-131-tositumomab are monoclonal antibodies that recognize the CD20 cell surface protein on normal and malignant B cells in follicular non-Hodgkin's lymphoma. Antibody binding to CD20 activates the immune system to attack and kill the cancerous B cells, and makes the cells more susceptible to chemotherapy. Iodine-131-tositumomab also targets radiation to the malignant B cells.