NOVEL TREATMENT OPTIONS FOR B-CELL MALIGNANCIES.

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During the past two decades, many novel therapies for the B-cell malignancies have been developed. Many of these agents have been used in the incurable indolent lymphomas (iL). Why do we need all of these new drugs? Indolent lymphomas are incurable disorders, patients experience repeated relapses, prolonged survival requires repeated good responses to new agents, and combinations are likely to be more effective than single agents. The wide array of novel therapies includes the following: (1) new monoclonal antibodies (mAb). Many of these have been humanized and have improved antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and increased apoptosis. Several of the newer mAb that are in phase II/III trials will be discussed. These include the following anti-CD20 mAb: ofatumumab, GA-101 and veltuzumab. Other non-CD20 mAb will be covered. (2) Immunomodulatory drugs (iMIDs), especially lenalidomide, that are finding an increasing role in the treatment of both iL and aggressive lymphomas. There are some promising findings in the use of lenalidomide in relapsed aggressive lymphomas. These iMIDs have recently been combined with rituximab for the frontline treatment of iL and chronic lymphocytic leukemia (CLL). (3) mTOR inhibitors have demonstrated efficacy not only in Waldenstrom's macroglobulinemia (WM) but in relapsed mantle cell (MCL) and iL. Trials are opening that are looking at mTOR inhibitors as maintenance treatment for high risk diffuse large B-cell lymphomas (DLBCL) that are in a complete remission after an R-CHOP regimen. (4) Other therapies to be discussed are apoptosis-inducing agents (ABT-263, obatoclax) and proteosome inhibitors. The proteosome inhibitor bortezomib is already approved for relapsed MCL, has efficacy in WM, related to the NFêÂ pathway. Bortezomib has efficacy in the activated B-cell (ABC) type of DLBCL and in combination with rituximab and bendamustine in iL. (5) Novel cytotoxic drugs including bendamustine have been discussed extensively at this meeting but have a special role in iL, CLL, MCL, and WM. (6) Other novel approaches include BiTE and small modular immuno-pharmaceuticals (SMIPs). Inhibitors of the B-cell gene receptor including SYK inhibitors and Btk inhibitors will be discussed. In summary, there are a multitude of novel approaches for B-cell malignancies, many targeting signaling pathways and the microenvironment of tumors.