Improved relative survival of patients with B-cell non-Hodgkin lymphoma in Queensland, 1993–2012

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Monoclonal antibody-based therapies are improving outcomes for patients with a range of cancers

Anti-cancer immunotherapy, including monoclonal antibodies to specific cell surface protein antigens, is proving to be a successful strategy in the emerging era of personalised medicine. This issue of the Journal includes the report of a retrospective study of the impact of one of the first therapeutic monoclonal antibodies, rituximab, on the relative survival of patients with non-Hodgkin lymphoma in Queensland between 1993 and 2012.1 Rituximab binds the CD20 antigen that is found on 90% of B cells, making it easier for other immune system cells to eliminate the cancerous cells (antibody-dependent cell-mediated immunity).

Wright, Hapgood and their co-authors report that adding rituximab to therapy improved the 5-year overall survival of patients with diffuse large B cell lymphoma (from 49% to 62%) or follicular lymphoma (from 73% to 86%), consistent with results reported from randomised clinical trials.1 Survival of patients with Hodgkin lymphoma did not change during the same period.1 Before the introduction of rituximab in 2003, nothing had improved the outcomes of intermediate grade lymphoma therapy since the introduction of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in the 1970s.

The population figures reported by Wright and colleagues lack detail regarding, for example, staging; as they recognise, prognostic factors and comorbid conditions may also influence outcomes. The influence of rurality and socio-economic status was examined, but the only statistically significant association was that survival of rural patients with diffuse large B-cell lymphoma was inferior to that of urban patients.1 However, the study was underpowered for achieving definitive findings. Patients in rural areas have previously been reported to have poorer outcomes than urban residents, but the differences may be influenced by other factors, such as the lower socio-economic status of rural regions.2

The study by Wright and colleagues shows that a small study population size makes subgroup analysis problematic. The major challenge of population studies is ensuring that outcomes are attributable to the treatment of interest and not to confounding factors, such as comorbid conditions and unrecognised changes in the study population. Better digitisation of our health data would facilitate linkage of clinical data with demographic and other population data, including clinical registry data, and would thus improve data accuracy and completeness.

Rituximab was one of the early successes in immunotherapy, but a range of further monoclonal antibodies have since been successfully applied to treating other cancers. For example, trastuzumab binds and downregulates the HER2 protein, the expression of which is amplified in 20% of breast cancers and in some gastric cancers, promoting cancer cell growth. Added to chemotherapy after surgery, trastuzumab increased the 10-year overall survival rate for women with operable HER2-positive breast cancer from 75% to 84%.3

Bispecific monoclonal antibodies combine two monoclonal antibodies to two different targets. Blinatumomab, used to treat relapsed acute lymphocytic leukaemia, binds to CD19 on leukaemic cells and CD3 on immune T cells, facilitating destruction of the leukaemic cells by the T cells. Long term survival (longer than 30 months) of patients treated with blinatumomab has been reported.4

Monoclonal antibodies can also be conjugated with a cytotoxic drug or radioactive isotope that they deliver to the cancer cells; in T-DM1, for example, trastuzumab is bound to the cytotoxic agent emtansine (DM1). As HER2 is overexpressed only by cancer cells, the toxin specifically targets these cells, and a meta-analysis found that T-DM1 was associated with improved overall survival of patients with metastatic breast cancer. Ibritumomab tiuxetan, the conjugate of an antibody to B-lymphocyte CD20 with yttrium-90, is employed as an adjunct in the treatment of relapsed or refractory non-Hodgkin lymphoma.6

Some other monoclonal antibody treatments do not target the cancer cells themselves. Bevacizumab, for example, targets vascular endothelial growth factor, blocking angiogenesis and preventing the new blood vessels forming around the tumour that are needed for its growth and spread. Bevacizumab improves the overall survival of patients with colorectal cancer or non-squamous lung cancer.7,8

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The most recent successes with monoclonal antibodies have been the checkpoint inhibitors — including ipilimumab, nivolumab, pembrolizumab, and atezolizumab — that block proteins on T cells or cancer cells which prevent the T cells targeting cancer cells. Ipilimumab binds to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on T lymphocytes, allowing an immune response in patients with advanced melanoma; a pooled analysis found 3-year survival to be 22%. Nivolumab and pembrolizumab block T cell programmed cell death protein 1 (PD-1), which helps prevent autoimmunity, but also inhibits their attacking cancer cells. These drugs have improved survival in patients with melanoma, have shown promise in the treatment of non-small cell lung cancer, and are being investigated for treating other cancers, including renal cancer and Hodgkin lymphoma. Side effects, however, include autoimmune effects in a range of organs. Atezolizumab, which blocks programmed death-ligand 1 (PD-L1) receptors on cancer cells, is being used to treat lung and bladder cancers.

As the study by Wright, Happgood and their co-authors indicates, rituximab is having an impact at the population level. Newer monoclonal antibodies are being tested for treating an increasing range of cancers, and it is expected that there will be further improvements in cancer survival at the population level.

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7 Botrel TE, Clark L, Paladini L, Clark O. Efficacy and safety of bevacizumab plus chemotherapy compared to chemotherapy alone in previously untreated advanced or metastatic colorectal cancer. BMC Cancer 2016; 16: 667.