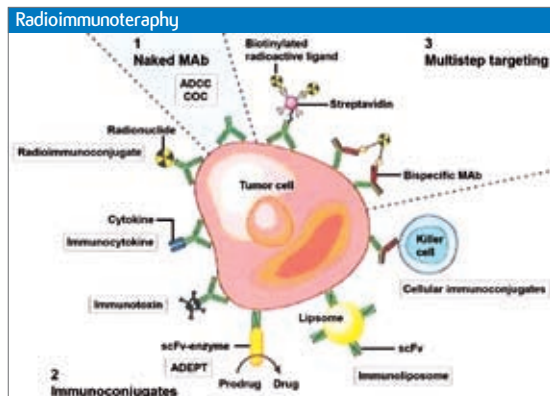


Radioimmunotherapy

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Radioimmunotherapy is a cancer treatment that combines the targeting power of monoclonal antibodies with the cell-damaging ability of localized radiation. These treatments are made by linking monoclonal antibodies - engineered in a laboratory to recognize and attach to substances on the surface of certain cells - to radioactive isotopes. When infused into a patient, these radiation-carrying antibodies circulate in the body until they locate and bind to the surface of specific cells, and then deliver their cytotoxic radiation directly to the cancerous cells. The first radio-labeled monoclonal antibody for B-cell lymphomas to be approved for human use was Zevalin, a murine IgG1 anti-CD20 monoclonal antibody that comes with two types of radiolabeling: One with Indium-111 (In-111) and one with Yttrium-90 (Y-90). We evaluated the efficacy and safety of a single dose of yttrium-90 (90Y) ibritumomab tiuxetan in elderly patients in first relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL) ineligible for stem-cell transplantation and demonstrate high response rates to 90Y-ibritumomab in relapsed DLBCL patients initially sensitive to chemotherapy and responses also in patients who were chemorefractory.



A prospective, multicenter, non-randomized phase 2 trial was conducted in collaboration with European research institutions. A total of 104 patients were enrolled in the study between September 2001 and October 2003. At the time we designed the study, data demonstrating the benefit of adding rituximab to CHOP chemotherapy were only just

beginning to emerge. Therefore, we divided the patients into 2 main groups depending on prior therapy: those who had previously received CHOP or a CHOP-like regimen alone (group A) or Rituximab plus CHOP or CHOP-like regimen (group B). Group A patients were further stratified based on whether they were induction failures (AI) or relapsed after having achieved a complete response (All). The overall response rate was 52% and 53% in strata AI and All, respectively, and 19% in group B, with CR/CRu rates of 24%, 39.5%, and 12%, respectively. Median progression-free survival was 5.9 months and 3.5 months in strata AI and All, respectively, and 1.6 months in group B. Median overall survival was 21.4, 22.4, and 4.6 months in stratum AI, stratum All, and group B, respectively. 90Y-ibritumomab induced high response rates in previously treated patients with DLBCL and in patients refractory to CHOP chemotherapy. Lower responses were observed after failure of R-CHOP than after failure of CHOP alone, although patients in the R-CHOP group generally had poorer prognostic features than those in the chemotherapy-alone group, and durable responses lasting longer than 2 years occurred in all patient groups. Furthermore, non-hematologic adverse events observed were mild to moderate. Studies integrating 90Y-ibritumomab into first-line immunochemotherapy regimens are currently under way, and will define the potential role of this agent in the overall management of DLBCL.

Another study carried out about diffuse large B-cell lymphoma (DLBCL) regards primary DLBCL of breast. It was the first large international retrospective study (204 patients) published about this uncommon primary site, comprising only 2% of localized extranodal NHL presentations.

It was conducted to define the specific features and outcomes of primary breast NHL aiming to incorporate the results into the design of a subsequent prospective study.

Information on all cases of primary breast NHL, from January 1980 to December 2003, presented by participating institutions, were collected retrospectively. Data were reviewed and all cases were reclassified according to

the WHO classification. Study-specific case record forms were provided and, as this was a retrospective study, staging procedures were not standardized, and not all variables were available for each patient. Thus, patients were staged according to the Ann Arbor classification. Certain common themes have emerged—diffuse large B-cell histology predominates, prognosis poorer than anticipated by stage, significant risk of contralateral breast involvement, and tendency to central nervous system relapse.

One unexpected finding was that the risk of central nervous system relapse was relatively low, occurring in only 5% of patients. This is at variance with the reports of other smaller retrospective series previously performed, and is considerably lower than the risk seen in primary testicular DLBCL. It may be that primary breast DLBCL does not have the same tropism for central nervous system as does testicular DLBCL, and that this difference explains the generally superior survival for patients with primary breast DLBCL compared with that of patients with primary testicular DLBCL. However, it is possible that limiting the eligibility to patients with localized disease has led to underestimation of the rate of central nervous system involvement.

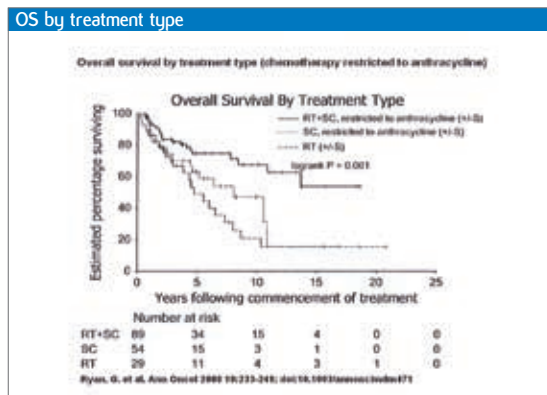
One factor found not to have prognostic significance was the extent of surgery—overall survival and progression-free survival were not improved with more extensive surgery, and radical mastectomy was actually associated with poorer cause-specific survival. This finding has been described in other series, and although it may be a statistical peculiarity, it is possible that extensive surgery delayed the commencement of chemotherapy, with unfavourable outcome.

Thus, the concept of radiotherapy improving survival in primary DLBCL of the breast is not necessarily contradictory with other prospective studies which concluded that the addition of radiotherapy to anthracycline-containing chemotherapy did not result in a survival benefit, and was possibly detrimental to survival, presumably as a result of late radiation toxicity.

Another important predictor of outcome was the inclusion of an anthracycline in the chemotherapy regimen, being significant for both overall survival and progression-free survival.

At that time, immunotherapy was not yet used and if Anthracycline-containing chemotherapy still remains a standard therapy, it is important that future prospective protocols for primary DLBCL of the breast incorporate Rituximab and perhaps other targeted therapies arising from further research.

OS by treatment type



Patients can successfully treated by a combination of chemotherapy and radiation. Because radiation to the breast, in the modern era, can be delivered with modest acute and late toxicity, and in such a situation, the potential for a positive benefit is substantially increased.