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(54) Title: TREATMENT OF PATIENTS HAVING NON-HODGKINS LYMPHOMA WITH BONE MARROW INVOLVEMENT WITH ANTI-CD20 ANTIBODIES

(57) Abstract: This invention relates to methods of reducing bone marrow involvement in B cell lymphoma patients prior to radioimmunotherapy by administering monoclonal antibodies which target cancerous B cells.

Treatment of Patients having Non-Hodgkins Lymphoma with Bone Marrow Involvement with Anti-CD20 Antibodies

Field of the Invention

The present invention relates to a method of reducing the number of cancerous B cells in the bone marrow of a patient having a B cell lymphoma prior to radioimmunotherapy comprising administration of an anti-CD20 antibody. Combined therapeutic methods of treating a patient having lymphoma with associated bone marrow involvement are also encompassed.

Background of the Invention

Radioimmunotherapy of B cell lymphoma is limited by marrow involvement, i.e., infiltration of the bone marrow by cancerous B lymphocytes. This complicates radioimmunotherapy in two regards: (1) antibody binding to diseased cells in the marrow will deliver a dose of radiation to the marrow thereby causing unwanted myelosuppression; and (2) marrow crowding of normal cells and progenitors will weaken healthy marrow reserves so that patients may actually be closer to grade 3 or 4 cytopenias than would be the case in patients without marrow involvement. In either case, the patient may be less tolerant to radioimmunotherapy, e.g., with B cell depleting antibody conjugated to a radioisotope such as ^{90}Y or ^{131}I. As a consequence, patients with greater than 25% bone marrow involvement

are generally excluded from treatment with radioimmunotherapy.

As found by Wiseman and colleagues, the clinical parameters of baseline platelet counts and degree of bone marrow involvement are accurate predictors of hematologic toxicity in patients with low-grade follicular non-Hodgkins lymphoma undergoing therapy with Y2B8, a murine anti-CD20 antibody conjugated to ^{90}Y. For instance, eight percent of patients (2/25) without bone marrow involvement developed Grade 4 thrombocytopenia vs. 25% (1/4) of those with 0.1-5% bone marrow involvement, 45% (5/11) of those with 5-20% involvement, and 100% (6/6) with 20-25% involvement (Wiseman et al. IDEC-Y2B8 radioimmunotherapy: baseline bone marrow involvement and platelet count are better predictors of hematologic toxicity than dosimetry. Blood 1998 Supplement November, 92(10): 417a (1721) Poster Board #/ Session: 393-III).

It would be useful to develop methods of reducing the marrow involvement in patients with non-Hodgkin's lymphoma such that these patients may benefit from new radioimmunotherapies, thereby providing another avenue of treatment and decreasing the chance of relapse. The present invention provides such methods.

Summary of the Invention

The present invention relates to methods of treating patients having B cell lymphoma accompanied by bone marrow involvement comprising administering a

monoclonal antibody or fragment thereof such that said bone marrow involvement is reduced or alleviated. Specifically, the invention encompasses methods of reducing the number of cancerous B cells in the bone marrow of a patient having non-Hodgkin's lymphoma prior to radioimmunotherapy comprising administering to said patient an effective amount of a therapeutic antibody. The methods are also useful for reducing bone marrow involvement prior to administration of antibodies labeled with cytotoxic moieties such as toxins, or any immunotherapeutic which could damage healthy bone marrow progenitors by virtue of their location in the vicinity of targeted cells which have infiltrated the bone marrow.

Preferably, anti-CD20 antibodies are used, although antibodies to other B cell surface markers may also be used, e.g., anti-CD19 antibodies. The cell surface protein which is targeted should have the characteristics of being expressed mainly on cancerous B cells and not generally on normal cells or B cell precursors, and preferably does not shed, internalize or modulate upon being bound by antibody.

The term antibody "fragments" includes any therapeutically effective portion or derivative of a therapeutic antibody, which is effective to bind to the intended target and produce the intended result. Included are Fab_2 fragments, Fab fragments, Fv fragments, domain-deleted antibodies, etc. Preferably, the antibodies used in the present invention are human,

chimeric or humanized antibodies, such that the antibodies contain human constant region domains capable of stimulating human effector functions. A preferred antibody is the chimeric anti-CD20 antibody, Rituximab® (marketed as Rituxan® in the U.S. and Mabthera® in Britain).

The patients who will most benefit from the present invention will be patients who have greater than 25% bone marrow involvement before being treated with the disclosed immunotherapy. Such patients may be identified by prior diagnostic imaging using antibodies radiolabeled with gamma-emitting isotopes such as ^{111}In. Such patients may also be identified following bone marrow biopsy.

According to a study by Wiseman et al., such patients have a very high chance of developing thrombocytopenia due to radioimmunotherapy. However, as the chance of developing such an adverse reaction following radioimmunotherapy increases depending on the extent of bone marrow involvement, any patient with any level of bone marrow involvement will benefit from the present invention in that they will benefit from a decreased risk of radioimmunotherapy-induced thrombocytopenia following the disclosed treatment.

The dosages to be used in the present invention may vary depending on the patient, the extent of bone marrow involvement, and the antibody used. Chimeric anti-CD20 antibody such as Rituximab® may be administered at a dosage of at least about 50 mg/m^2 weekly for at least 4

weeks. A preferred dosage regimen is about 375 mg/m^2 weekly for four weeks.

Because the purpose of the methods of the present invention is to decrease the bone marrow involvement in patients with lymphoma preparing to undergo radioimmunotherapy, the treatment methods of the present invention naturally encompass treatment with a radiolabeled antibody subsequent to purging of the marrow. The radiolabeled antibody may also be directed to any B cell surface marker which is found generally on cancerous cells and not normal cells. Preferably, the radiolabeled antibody is an anti-CD20 antibody.

Preferred radiolabels are beta emitting isotopes such as ^{90}Y or ^{131}I, but any radioisotope may be used so long as it may be effectively conjugated to the antibody, it has a relatively short decay range, and it succeeds in killing nearby cells, i.e., the cells to which it is targeted. A preferred radiolabeled anti-CD20 antibody is Y2B8.

A patient should generally be treated within one week after administration of the depleting antibody, so long as they are not severely cytopenic, e.g., platelets <150,000. If the patient is cytopenic following treatment with the depleting antibody, recovery should be allowed to occur, e.g. nadir AGC >1000 or platelets >150,000, before radioimmunotherapy. In cases where cell recovery in the peripheral blood and/or bone marrow is permitted to occur, more depleting antibody may be administered directly before immunotherapy. Such a

secondary dosage may be administered, for example, at about 250 mg/m^2 for about two weeks directly before or overlapping with radioimmunotherapy.

Dosages of radiolabeled antibodies will also vary depending on the patient, the antibody specificity, half-life, stability, etc., and of course, the extent of disease. Radiolabeled anti-CD20 antibodies like Y2B8 are administered at a dosage of about 0.1 to 0.5 mCi/kg.

It should be clear that the treatment methods disclosed herein may be combined with other known treatment methods such as chemotherapy or radiotherapy. Bone marrow or peripheral blood stem cells may be harvested from said patient subsequent to treatment with anti-CD20 antibody and prior to treatment with said radiolabeled antibody in order to effect autologous bone marrow or stem cell transplantation after radiotherapy.

It may also be useful to treat patients with cytokines in order to upregulate the expression of CD20 or other target protein on the surface of cancerous B cells prior to administration of the depleting antibody or the radiolabeled antibody. For upregulation of CD20, cytokines useful for this purpose are IL-4, GM-CSF and TNF-alpha. Cytokines may also be administered simultaneously with or prior to or subsequent to administration of the depleting antibody or radiolabeled antibody in order to stimulate immune effector functions. Cytokines useful for this purpose include interferon alpha, GM-CSF and G-CSF.

Chemotherapeutic regimens may be used to supplement the therapies disclosed herein, and may be administered simultaneously with or sequentially in any order with administration of said radiolabeled antibody. The chemotherapy regimen may be selected from the group consisting of CHOP, ICE, Mitozantrone, Cytarabine, DVP, ATRA, Idarubicin, hoelzer chemotherapy regime, La La chemotherapy regime, ABVD, CEOP, 2-CdA, FLAG & IDA (with or without subsequent G-CSF treatment), VAD, M & P, C-Weekly, ABCM, MOPP and DHAP. A preferred chemotherapeutic regimen is CHOP.

The methods of the present invention may be used to treat a variety of B cell lymphomas but are particularly useful wherein said B cell lymphoma is non-Hodgkin's lymphoma (NHL). Rituximab® has already been approved for the treatment of low-grade-follicular NHL, but the present inventors have surprisingly found that Rituximab® is also beneficial for the treatment of intermediate- and high-grade NHL, including bulky disease. Accordingly, the lymphomas which are treatable by the methods of the present invention include low grade/ follicular non-Hodgkin's lymphoma (NHL), small lymphocytic (SL) NHL, intermediate grade/ follicular NHL, intermediate grade diffuse NHL, chronic lymphocytic leukemia (CLL), high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small noncleaved cell NHL, bulky disease NHL, mantle cell lymphoma, AIDS-related lymphoma and Waldenstrom's Macroglobulinemia, so long as such lymphomas are accompanied by bone marrow

involvement which complicates the availability of radioimmunotherapy.

Exemplary treatment conditions will now be illustrated by way of the following data.

Radioimmunotherapy of Relapsed or Refractory Non-Hodgkin's Lymphoma (NHL): Y2B8 Phase I/ II ^{90}Y Trial

This Phase I/II trial included 58 relapsed or refractory NHL patients, median age 60, 43% bone marrow involvement, 60% bulky lesions > 5 cm (White et al. Poster Presentation at VII International Conference on Malignant Lymphoma, Lugano, Switzerland. Annals of Oncology Suppl. 3 (1999) 10:64(215)). All patients had dosimetry by gamma camera measurements and by serial urine and blood sampling following administration of 5 mCi of ^{111}In-labeled antibody In2B8. Prior to imaging and therapy, Rituximab® was used to clear peripheral B-cells and optimize radiolabeled antibody distribution. One week later, Y2B8 (0.2, 0.3 or 0.4 mCi/kg) was administered to Group 2 & 3 patients. No bone marrow or stem cell harvest was performed.

Results:

The MTD was 0.4 mCi/kg (0.3 mCi/kg for patients with mild thrombocytopenia). Adverse events were mainly hematologic, transient and reversible. Overall, 5 patients (10%) developed nadir platelet counts <10,000/mm^3 and 14 patients (28%) developed nadir AGC <500. Three patients (6%) acquired infections requiring

hospitalization over a one year observation period. Only 2% developed HAMA/HACA. Mean serum immunoglobulins remained normal over a one year observation period. The ORR was 67% (26% CR and 41% PR) in all histologies and 82% for patients with low-grade NHL. The median TTP was 12.9+ months for responders, and the duration of response was 11.7+ months as projected by Kaplan Meier methodology. In patients with baseline splenomegaly, 4/8 (50%) patients responded compared to 74% (29/39) without splenomegaly (p= 0.1761). Two clinical parameters, baseline platelet counts and degree of bone marrow involvement in baseline biopsy, were better at predicting severity of hematologic toxicity than dosimetry parameters.

What is Claimed:

1. A method of treating a patient having B cell lymphoma accompanied by bone marrow involvement comprising administering an anti-CD20 antibody or fragment thereof such that said bone marrow involvement is reduced or alleviated.

2. The method of claim 1, wherein said bone marrow involvement is initially greater than 25%.

3. The method of claim 2, wherein said treatment reduces said bone marrow involvement to less than 25%.

4. The method of claim 1, wherein said anti-CD20 antibody is a human, chimeric or humanized antibody.

5. The method of claim 4, wherein said anti-CD20 antibody is a chimeric anti-CD20 antibody.

6. The method of claim 5, wherein said chimeric anti-CD20 antibody is Rituximab®.

7. The method of claim 6, wherein said chimeric anti-CD20 antibody is administered at a dosage of at least about 50 mg/m^2 weekly for at least 4 weeks.

8. The method of claim 7, wherein said chimeric anti-CD20 antibody is administered at a dosage of about 375 mg/m^2 weekly for four weeks.

9. The method of claim 1, further comprising subsequent administration of a radiolabeled antibody.

10. The method of claim 9, wherein said radiolabeled antibody is an anti-CD20 antibody.

11. The method of claim 10, wherein said radiolabeled anti-CD20 antibody is Y2B8.

12. The method of claim 11, wherein said radiolabeled anti-CD20 antibody is administered at a dosage of about 0.1 to 0.5 mCi/kg.

13. The method of claim 9, wherein additional anti-CD20 antibody is administered simultaneously with or sequentially in either order with said radiolabeled antibody.

14. The method of claim 13, wherein at least a single dosage of said additional anti-CD20 antibody is administered as at a dosage of about 250 mg/m^2.

15. The method of claim 9, wherein bone marrow or peripheral blood stem cells are harvested from said patient subsequent to treatment with anti-CD20 antibody and prior to treatment with said radiolabeled antibody.

16. The method of claim 1, wherein expression of CD20 is upregulated on the surface of cancerous B cells

prior to administration of said anti-CD20 antibody by administering at least one cytokine.

17. The method of claim 16, wherein said cytokine is selected from the group consisting of IL-4, GM-CSF and TNF-alpha.

18. The method of claim 9, further comprising treatment with a chemotherapeutic regimen simultaneously with or sequentially in any order with administration of said radiolabeled antibody.

19. The method of claim 19, wherein said chemotherapy is selected from the group consisting of CHOP, ICE, Mitozantrone, Cytarabine, DVP, ATRA, Idarubicin, hoelzer chemotherapy regime, La La chemotherapy regime, ABVD, CEOP, 2-CdA, FLAG & IDA (with or without subsequent G-CSF treatment), VAD, M & P, C-Weekly, ABCM, MOPP and DHAP.

20. The method of claim 19, wherein the chemotherapeutic regimen is CHOP.

21. The method of claim 1, further comprising administration of at least one cytokine simultaneously with or sequentially in either order with said anti-CD20 antibody.

22. The method of claim 22, wherein said at least one cytokine is selected from the group consisting of interferon alpha, GM-CSF and G-CSF.

23. The method of claim 1, wherein said B cell lymphoma is non-Hodgkin's lymphoma (NHL).

24. The method of claim 23, wherein said NHL is selected from the group consisting of low grade/ follicular non-Hodgkin's lymphoma (NHL), small lymphocytic (SL) NHL, intermediate grade/ follicular NHL, intermediate grade diffuse NHL, chronic lymphocytic leukemia (CLL), high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small noncleaved cell NHL, bulky disease NHL, mantle cell lymphoma, AIDS-related lymphoma and Waldenstrom's Macroglobulinemia.

25. A method of reducing the number of cancerous B cells in the bone marrow of a patient having non-Hodgkin's lymphoma prior to radioimmunotherapy comprising administering to said patient an effective amount of anti-CD20 antibody.

26. The method of claim 25, wherein said anti-CD20 antibody is a human antibody, a chimeric antibody or a humanized antibody.

27. The method of claim 26, wherein said antibody is a chimeric antibody.

28. The method of claim 27 wherein said chimeric antibody is Rituximab®.

29. The method of claim 25, wherein said chimeric anti-CD20 antibody is administered at a dosage of at least about 50 mg/m^2 weekly for at least 4 weeks.

30. The method of claim 29, wherein said chimeric anti-CD20 antibody is administered at a dosage of about 375 mg/m^2 weekly for four weeks.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/40459

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 39/395

US CL : 424/ 130.1, 138.1, 141.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/ 130.1, 138.1, 141.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,595,721 A (KAMINSKI et al) 21 January 1997 (21.01.1997), abstract, columns 1,5,7,9-10,13,15,30-31,33	1,4-5,9-10,13,15,18-19,23-27 --- 21-22
X --- Y	US 5,843,439 A (ANDERSON et al.) 01 December 1998 (01.12.1998), columns 1-4, 27-28, 30 columns 28-30	19,25-27,29-30 --- 1,4-5,8-11,13-14
X,P	GOPAL et al., Clinical Applications of anti-CD20 antibodies, J.Lab.Clin.Med. November 1999, Vol. 134, entire document.	25-30
X	MALONEY et al., Newer Treatments for Non-Hodgkin's Lymphoma: Monoclonal Antibodies, Oncology, October 1998, Vol. 12. No. 8, abstract and pages 65-68.	19-20, 25-30
A,P	WISEMAN, et al. Radioimmunotherapy of Relapsed Non-Hodgkin's lymphoma with Zevalin, a Y-labled Anti-CD20 Monoclonal Antibody. Clin.Can.Res., October 1999, Vol. 5. entire document.	1,25-27

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/40459

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	BEHR et al., Low- versus High-Dose Radioimmunotherapy with Humanized Anti-CD22 or Chimeric Anti-CD20 Antibodies in a Broad Spectrum of B Cell-associated Malignancies. Clin.Can.Res., October 1999, Vol. 5. entire document.	1,25-27
A,P	WITZIG et al., Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma., J.Clin.Oncol., December 1999, Vol. 17. No. 12, abstract only.	11-12, 25-27