Summary of the Invention

Surprisingly we have now found out that the combination of fludarabine and/or mitoxantrone (especially the in vivo combination of fludarabine) with an afucosylated anti-CD20 antibody showed synergistic (e.g. more than additive in some cases) antiproliferative effects compared to the combination with non-afucosylated CD20 antibody rituximab.

In one aspect, there is provided the use of an afucosylated anti-CD20 antibody with an amount of fucose of 60 % or less of the total amount of oligosaccharides (sugars) at Asn297, for the manufacture of a medicament for the treatment of cancer in combination with fludarabine wherein said antibody is a humanized B-Ly1 antibody, and the humanized B-Ly1 antibody is characterized in comprising an amino acid sequence of the variable region of the heavy chain (VH) of SEQ ID NO: 7 (B-HH6), and in comprising an amino acid sequence of the variable region of the light chain (VL) of SEQ ID NO: 20 (B-KV1); and wherein said cancer is a B-Cell Non-Hodgkin's lymphoma (NHL).

In another aspect, there is provided the use of an afucosylated anti-CD20 antibody with an amount of fucose of 60 % or less of the total amount of oligosaccharides (sugars) at Asn297, for the manufacture of a medicament for the treatment of cancer in combination with fludarabine wherein said antibody is a humanized B-Ly1 antibody, and the humanized B-Ly1 antibody is characterized in comprising an amino acid sequence of the variable region of the heavy chain (VH) of SEQ ID NO: 7 (B-HH6), and in comprising an amino acid sequence of the variable region of the light chain (VL) of SEQ ID NO: 20 (B-KV1); and wherein said cancer is a B-Cell Non-Hodgkin's lymphoma (NHL); and wherein the humanized B-Ly1 antibody is administered in a dosage of 800 to 1600 mg on day 1 of up to six or seven 3-to 4-week-dosage-cycles, and fludarabine is administered in a dosage of 20mg/m^2 to 30 mg/ m^2 on day 1, 2 and 3 of up to six or seven 4-week-dosage-cycles.

The ~~the~~ disclosure~~invention~~ comprises the use of an afucosylated anti-CD20 antibody with an amount of fucose of 60 % or less of the total amount of oligosaccharides (sugars) at Asn297, for the manufacture of a medicament for the treatment of cancer in combination with fludarabine and/or mitoxantrone.

The disclosure may relate to~~One aspect of the invention is~~ a method of treatment of patient suffering from cancer by administering an afucosylated anti-CD20 antibody with an amount of fucose of 60 % or less of the total amount of oligosaccharides (sugars) at Asn297, in combination with fludarabine and/or mitoxantrone, to a patient in the need of such treatment.

The disclosure may relate to~~Another aspect of the invention is~~ an afucosylated anti-CD20 antibody with an amount of fucose of 60 % or less of the total amount of oligosaccharides (sugars) at Asn297, for the treatment of cancer in combination with fludarabine and/or mitoxantrone.

In one embodiment, the amount of fucose is between 40 % and 60 % of the total amount of oligosaccharides (sugars) at Asn297.

In another embodiment, the amount of fucose is 0% of the the total amount of oligosaccharides (sugars) at Asn297.

In one embodiment, the afucosylated anti-CD20 antibody is an IgG1 antibody.

In another embodiment, said afucosylated anti-CD20 antibody is humanized B-Ly1 antibody, and said cancer is a CD20 expressing cancer, which in one embodiment is a B-Cell Non-Hodgkin's lymphoma (NHL).

In one embodiment, the afucosylated anti-CD20 antibody binds CD20 with an KD of 10^{-9} M to 10^{-13} mol/l.

In one embodiment the treatment of cancer is in combination with fludarabine.

In one embodiment the treatment is characterized in that the humanized B-Ly1 antibody is administered in a dosage of 800 to 1600 mg on day 1 of up to six or seven 3-to 4-week-dosage-cycles, and fludarabine is administered in a dosage of 20mg/m^2 to 30 mg/ m^2 on day 1, 2 and 3 of up to six or seven 4-week-dosage-cycles.

In one embodiment the treatment is in combination with fludarabine and cyclophosphamide.

In one embodiment the treatment of cancer is characterized in that the humanized B-Ly1 antibody is administered in a dosage of 800 to 1600 mg on day 1 of up to six or seven 3-to 4-week-dosage-cycles, fludarabine is administered in a dosage of 20mg/m^2 to 30 mg/ m^2 on day 1, 2 and 3 of up to six or seven 4-week-dosage-cycles, and cyclophosphamide is administered in a dosage of 200 mg/m^2 to 300 mg/ m^2 on day 1, 2 and 3 of up to six or seven 4-week-dosage-cycles.

In one embodiment the treatment of cancer is in combination with mitoxantrone.

In one embodiment the treatment of cancer is characterized in that one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation that enhance the effects of such agents are administered.

One embodiment of the disclosure~~invention~~ is a composition comprising an anti-CD20 afucosylated antibody with an amount of fucose of 60 % or less, and fludarabine and/or mitoxantrone (preferably fludarabine) for the treatment of cancer.

Detailed Description of the Invention

The invention comprises the use of an afucosylated anti-CD20 antibody (of IgG1 or IgG3 isotype, preferably of IgG1 isotype) with an amount of fucose of 60 % or less of the total amount of oligosaccharides (sugars) at Asn297, for the manufacture of a medicament for the treatment of cancer in combination with fludarabine and/or mitoxantrone.

In one embodiment, the amount of fucose is between 40 % and 60 % of the total amount of oligosaccharides (sugars) at Asn297.

The term "antibody" encompasses the various forms of antibodies including but not being limited to whole antibodies, human antibodies, humanized antibodies and genetically engineered antibodies like monoclonal antibodies, chimeric antibodies

Patent Claims

1. Use of an afucosylated anti-CD20 antibody with an amount of fucose of 60 % or less of the total amount of oligosaccharides (sugars) at Asn297, for the manufacture of a medicament for the treatment of cancer in combination with fludarabine ~~and/or mitoxantrone~~ wherein said antibody is a humanized B-Ly1 antibody, and the humanized B-Ly1 antibody is characterized in comprising an amino acid sequence of the variable region of the heavy chain (VH) of SEQ ID NO: 7 (B-HH6), and in comprising an amino acid sequence of the variable region of the light chain (VL) of SEQ ID NO: 20 (B-KV1); and wherein said cancer is a B-Cell Non-Hodgkin's lymphoma (NHL).

2. Use according to claim 1, characterized in that the treatment of cancer is in combination with fludarabine.

3. Use according to claim 2 characterized in that the humanized B-Ly1 antibody is administered in a dosage of 800 to 1600 mg on day 1 of up to six or seven 3-to 4-week-dosage-cycles, and fludarabine is administered in a dosage of 20mg/m^2 to 30 mg/ m^2 on day 1, 2 and 3 of up to six or seven 4-week-dosage-cycles.

4. Use according to claim 1, characterized in that the treatment of cancer is in combination with fludarabine and cyclophosphamide.

5. Use according to claim 4 characterized in that the humanized B-Ly1 antibody is administered in a dosage of 800 to 1600 mg on day 1 of up to six or seven 3-to 4-week-dosage-cycles, fludarabine is administered in a dosage of 20mg/m^2 to 30 mg/ m^2 on day 1, 2 and 3 of up to six or seven 4-week-dosage-cycles, and cyclophosphamide is administered in a dosage of 200 mg/m^2 to 300 mg/ m^2 on day 1, 2 and 3 of up to six or seven 4-week-dosage-cycles.