Association between deficiency of mannose-binding lectin and severe infections after chemotherapy

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The plasma protein mannose-binding lectin (MBL) activates the complement system by binding to carbohydrate structures presented by microorganisms and thus could be an important component of the innate immune defence system. We measured MBL in patients with leukaemia who were scheduled to undergo chemotherapy (ie, a population especially susceptible to infection) and related the results to severity of infection after chemotherapy. We showed a significant association between low concentrations of MBL and serious infections related to chemotherapy (p<0·0001). These results suggest that increasing concentrations of MBL in patients having chemotherapy could reduce susceptibility to infection.

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Cancer chemotherapy causes immunosuppression and serious infections can result. These infections might compromise the effectiveness of chemotherapy as they might lead to delay or reduction in chemotherapy. Neutropenia and hypogammaglobulinaemia are known risk factors for infections in cancer patients. We postulated that deficiency of mannose-binding lectin (MBL) could also play a part.

MBL is part of the innate immune system, and deficiency of this plasma protein is a common abnormality of host defence. It binds to carbohydrate structures on the surface of microorganisms (including bacteria, viruses, and fungi) and mediates deposition of complement factors. The deposition causes destruction of the microorganism via the membrane attack complex and through enhanced phagocytosis due to the opsonising effect of C3b.

The clinical importance of MBL was first understood when a deficiency of this protein was identified as the probable cause of opsonin deficiency in children with unexplained propensity for frequent, generally serious infections. Subsequent epidemiological investigations have supported this finding. MBL-reactive carbohydrate epitopes occur on the surface of several cancer cell lines, and we therefore investigated whether there might be a general over-representation of MBL deficiency in patients with malignant haematological diseases.

We investigated 54 adult patients from Jutland, Denmark. 18 (33%) patients had multiple myeloma, 13 (24%) had non-Hodgkin’s lymphoma, seven (13%) had acute myeloid leukaemia, five (9%) each had chronic lymphocytic leukaemia or Hodgkin’s lymphoma, two (4%) had chronic myeloid leukaemia, and one patient each (2%) had Burkitt’s lymphoma, Waldenström’s macroglobulinaemia, acute lymphoid leukaemia, or
a aplastic anaemia. Patients were treated with appropriate standard regimens: multiple myeloma—vincristine, doxorubicin, and dexamethasone, or mitoxantrone, vincristine, and prednisone, or melphalan and prednisone; acute myeloid leukaemia—idarubicin and cytarabine; non-Hodgkin lymphoma—cyclophosphamide, doxorubicin, vincristine, and prednisone; Waldenström’s macro-globulinaemia—cladribicul, and prednisone; acute lymphoid leukaemia—cyclophosphamide, vincristine, daunorubicin, L-asparaginase, and intraspinal methotrexate; aplastic anaemia—antithymocyte globulin, prednisolone, and ciclosporin A.

We identified patients who contracted clinically important infections—defined as bacteremias (ie, positive blood culture) (three patients), pneumonia (ten), or both (three) within 3 weeks from start of chemotherapy (for the subgroup of patients with multiple myeloma, the numbers were six, one, and one, respectively)—using a retrospective computer search of the general patient database. A 3-week interval was chosen to reduce confounding due to variations in length of neutropenia. The investigation was done in accordance with the recommendations of the Helsinki declaration.

MBL was measured by time-resolved immuno-fluorometric assay on edetic acid plasma samples obtained from blood taken before patients started chemotherapy. Microwells coated with anti-MBL antibody were incubated with dilutions of patient plasma, were developed with europium-labelled anti-MBL antibody, and europium was quantified with time-resolved fluorometric assay.

The distribution of MBL concentrations in all patients with haematological disease was compared with that seen in a comparison group of 100 apparently healthy local blood donors8 with Mann-Whitney rank sum analysis. No significant difference was seen (p=0.179). However, significantly lower concentrations of MBL were seen in patients who had clinically important infections as compared to those without infections (p<0.0001). There was an increased susceptibility to infections in patients with an MBL concentration of about 500 µg or less (figure). An analysis restricted to patients with multiple myeloma (n=8) showed a similar difference (p=0.0059) (figure).

Previous studies of a possible correlation between MBL deficiency and frequency of infection have used an arbitrary concentration for deficiency, usually the lower level of detection of the assay (eg, 10 µg). There are no clinical data for choosing this cutoff to define deficiency. Many investigators, have related disease to frequency of infection indicated what was a clinically relevant concentration of MBL. Surprisingly, in this specific patient population a biologically normal range of MBL concentration might be associated with increased risk of infection.

Preliminary results5 have shown the safety of MBL infusions in MBL deficient individuals. Our findings suggest that patients with low MBL concentrations could benefit from replacement therapy with MBL before and during chemotherapy.

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