Selected Summaries

Lymphocytosis and chronic leukaemia

Rawstron AC, Bennett FL, O'Connor SJ, Kwok M, Fenton JA, Plummer M, de Tute R, Owen RG, Richards SJ, Jack AS, Hillmen P. (Haematological Malignancy Diagnostic Service, Leeds Teaching Hospitals, Leeds, United Kingdom.) Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. *N Engl J Med* 2008;**359:**575–83.

SUMMARY

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia among the elderly in the developed world. It is less frequent in India and other developing countries, but its incidence is increasing possibly as a result of a longer lifespan and changing lifestyle.[1] The diagnosis of CLL requires an absolute lymphocyte count of ≥5000/cmm with the presence of monoclonality evidenced by characteristic cell-surface phenotype of B cells on flow cytometry: the presence of CD19, CD5 and CD23; weak expression of CD20 and CD79b; and either kappa or lambda immunoglobulin light chains.[2] Some adults (3%) who have an absolute lymphocyte count of <5000/cmm but express CLL-like cell surface phenotype are said to have 'monoclonal B-cell lymphocytosis (MBL) of uncertain significance'. The biological importance of this finding is unclear.[3]

In this study, Rawstron *et al*. studied two cohorts—one comprising 1520 subjects with normal blood counts and the other of 2228 subjects with lymphocytosis (defined as >4000 lymphocytes/cmm) for the presence of monoclonal B-cell population using flow cytometry. Cytogenetic and molecular characterization of the monoclonal B-cell population was done and a small group of 185 subjects with MBL was followed for a median period of 6.7 years (range: 0.2–11.8 years).

The first cohort had persons 60–80 years of age who were attending outpatient departments of various specialties except haematology, oncology and a transplant clinic and they had a normal total leucocyte count, platelet count and haemoglobin. The second cohort consisted of subjects referred for current or previous lymphocytosis between April 1995 and December 2000.

Among the first cohort (normal blood counts), 78 (5.1%) were found to have CLL-phenotype MBL and 27 (1.8%) had non-CLL-phenotype MBL. In the second cohort, 309 (13.9%) had CLL-phenotype MBL and the rest had CLL (46.3%) or reactive lymphocytosis (39.9%).

Of the 71 subjects with CLL-phenotype MBL in either cohort (analysed by FISH), 13q14 del, trisomy 12, 11q23 del and 17p del were detected in 39% ,18%, 0% and 0% in the first cohort with normal blood counts, and in 58%, 21%, 6% and 3% in the second cohort (with lymphocytosis). Immunoglobulin heavy variable group (IGHV) mutation was detected in 85% of the subjects with MBL with normal counts and 90% of those with MBL with lymphocytosis. Follow up was not available for those with MBL and normal counts as the samples were anonymous. However, 185 of the subjects with MBL and lymphocytosis (second cohort) were followed for 6.7 years; progressive lymphocytosis developed in 51 (28%) of these. Among those with progressive lymphocytosis, further evidence of progressive CLL (lymphadenopathy, hepatomegaly, splenomegaly, lymphocyte doubling time <6 months and drenching sweats) developed in 28 (55%). Thirteen of the 51 subjects eventually required chemotherapy. Baseline B-cell count was the only factor that predicted progressive lymphocytosis; subjects with a baseline B-cell count <1900/cmm rarely progressed.

COMMENT

MBL is defined by the presence in the blood of <5000/cmm monoclonal B cells in the absence of signs and symptoms of CLL or any other lymphoproliferative or autoimmune disease.[3] MBL is a relatively new diagnostic category which signifies the development of a monoclonal B-cell population with advancing age. Phenotypically heterogeneous monoclonal B-cell expansions are common among healthy elderly individuals probably due to a deterioration in immunological surveillance with advancing age.[4] It is important to identify and distinguish MBL from CLL as CLL-type MBL may not necessarily progress to CLL and all that may be required is monitoring.

Various studies have suggested the presence of monoclonal B cells with phenotypic characteristics similar to CLL.[5,6] Rawstron *et al*. reported a 3.5% incidence of MBL in adults with normal blood counts.[5]

In this study with a relatively large sample size, it has been shown that elderly people with normal blood counts may also have MBL (5.1%) and the incidence of MBL increases in people with lymphocytosis (13.9%). It is interesting that the incidence of chromosomal abnormalities (13q14, trisomy 12 in CLL-phenotype MBL) in people with lymphocytosis is similar to that in CLL. However, high risk abnormalities such as 11q23 and 17p del are less frequent (9% *v*. 25%), indicating that MBL may be a precursor for developing CLL and high risk chromosomal abnormalities may cause progression. An unmutated immunoglobulin heavy chain variable gene region is a high risk factor for CLL. In MBL the incidence of unmutated immunoglobulin was 13% compared with 58% in CLL.[5,6] It is of interest that MBL is a precursor of CLL just as monoclonal gammopathy of unknown significance (MGUS) is of multiple myeloma.[7] In both cases, clonal expansion of abnormal cells (mature lymphocytes in CLL and plasma cells in myeloma) is the defining feature. The annual risk of developing CLL requiring chemotherapy in subjects with a CLL-phenotype MBL was calculated to be 1%–2%. This is similar to the rate of progression of MGUS to multiple myeloma.[7] A majority of deaths occurring in CLL-phenotype MBL are due to unrelated causes. Of the 62 subjects who died, 13 had progressive CLL and in only 4 was CLL the cause of death.[8]

Thus, MBL represents a premalignant condition and about 1% of adults with MBL may progress to CLL every year; the risk of developing CLL is higher in those who have high baseline B-cell counts. Such persons should be closely monitored. Considering the variable course of CLL (one-third of patients have early stage [Rai stage 0 and I], one-third have intermediate stage [Rai stage II] and the remaining one-third have advanced stage [Rai stage III–IV]), this does not seem to be a cause for concern. Presently, for CLL patients with Rai stage 0–I, close monitoring is advised. Such patients have a median survival of >13 years.[9] This study has provided the link between MBL and the development of CLL as a result of additional oncogenic events. Senescence-related diminution of immune surveillance could be another possibility.[10] Understanding the mechanism of the clonal proliferation of cells and steps involved in the progression from

MBL to CLL would be possible areas of research in the future.

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The role of mechanical bowel preparation before colorectal surgery

Slim K, Vicaut E, Launay-Savary MV, Contant C, Chipponi J. (Department of General and Digestive Surgery, Hôtel-Dieu, Clermont-Ferrand, France.) Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. *Ann Surg* 2009;**249:**203–9.

SUMMARY

Despite evidence challenging the ritual of mechanical bowel preparation (MBP) before colorectal surgery for over 3 decades, MBP is still performed by a majority of colorectal surgeons. The bulk of evidence demonstrating a detrimental effect of MBP was based on small trials. Recently, 2 large multicentre trials evaluating the role of MBP, each recruiting over 1300 patients, have been published. Hence, it was important to re-evaluate the evidence in the light of recently published trials incorporating all the currently available information on the subject.

The authors did a meta-analysis after doing a systematic search of the published as well as unpublished data without any time period or language restrictions using both manual search and electronic databases. Two independent reviewers selected randomized clinical trials once all the items of the QUOROM checklist were satisfied and the methodological quality of the included trials was assessed using a previously validated score. The score ranged from 0 to 5 and the methodological quality of a trial was considered poor when the score was 2 or less. The primary outcome measure was anastomotic leakage and the secondary outcomes included other infectious complications (pelvic abscess, peritonitis and wound infection), overall surgical site infection (SSI), re-operations, extra-abdominal infections (broncho-pulmonary, urinary), hospital stay and mortality. The outcomes were analysed on an intention-to-treat basis using the Peto method. A total of 87 trials were retrieved of which 73 were excluded due to various reasons and eventually 14 trials containing 4859 patients (MBP=2452 and no MBP=2407) were included in the meta-analysis. The funnel plot for primary outcome measure was symmetrical indicating a lack of publication bias. Based on the quality score, the quality of 3 trials was classified as suboptimal. The meta-analysis revealed the following:

1. Overall, there was no significant difference between those receiving and not receiving MBP with regard to the primary outcome measure, i.e. anastomotic leak (OR: 1.12, p=0.46).
2. No significant difference existed between secondary outcome measures with the exception of overall incidence of SSI which favoured no MBP (OR: 1.4, p=0.02).
3. There was no significant difference with regard to any outcome measure when analysis was stratified according to the type of solution used (polyethylene glycol or sodium phosphate).
4. When 3 trials with suboptimal quality were excluded from the analysis, the results did not change with the exception of abdominal abscess formation with a significant difference in favour of MBP (OR: 0.55, p=0.01) and this effect size became even more pronounced when only 2 large trials each recruiting over 1300 patients were analysed (OR: 0.46, p=0.004).
5. Because of a small number of patients stratified according to the level of anastomosis (200 in each arm) and a variety of solutions used, a formal meta-analysis could not be done with regard to rectal surgery.

COMMENT

The current meta-analysis highlights the methodological flaws and suboptimal quality of randomized controlled trials reported in the surgical literature, and underlines the pressing need to conduct well planned, methodologically sound clinical trials. The reliability of a meta-analysis is dependent on the quality of the trials included. The results of earlier meta-analyses reporting detrimental effects of MBP were influenced by the small and heterogeneous trials of relatively low quality.[1–4] Even in the current meta-analysis, of the 14 included trials, an important methodological variable such as sample size calculation was reported in only 5 trials (30%) and even among these 5 trials, the sample size calculated was based on the primary outcome measure of meta-analysis (anastomotic leakage) in only 1 trial.[5] The inclusion of underpowered studies increases the possibility of introducing a type 2 error in the results of a meta-analysis as well. Moreover, the length of follow up is important in defining SSI and for this