MINIMAL RESIDUAL DISEASE, ITS DETECTION AND SIGNIFICANCE IN HAIRY-CELL LEUKEMIA

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Summary: As minimal residual disease (MRD) is considered the detection of hairy cells (HCS) in a patient with hairy cell leukemia (HCL) in complete remission with the absence of detectable HCs by routine morphology of peripheral blood, aspirates and bone marrow core sections, using more sensitive methods of identification as immunohistological staining or polymerase chain reaction (PCR) to detect immunoglobulin heavy chain genes rearrangement. Various monoclonal antibodies (MoAbs) as CD20, DBA 44, B ly-7, HC2, CD25 and CD11c have been applied using immunological staining. There is no standardized technique for identification of MRD. According to the technique used the MRD has been detected in 13% to 100% of patients in complete remission (CR). It may be concluded that many patients, if not all, in stable CR may have residual HCs. Whether MRD will have impact on early relapse or on long term outcome, or whether patients in CR with persistant MRD will remain so, is a matter of a longer follow-up.

Key words: Hairy cell leukemia; Minimal residual disease; Detection; Significance

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Introduction

Hairy cell leukemia (HCL) is a clonal chronic lymphoproliferative disorder characterized by pancytopenia, splenomegaly without significant lymphadenopathy, and by abnormal mononuclear cells of B cell origin infiltrating bone marrow and spleen (15). It is a distinct clinical and pathological entity (5). Although the disease is relatively indolent, the majority of patients require treatment for life-threatening pancytopenia or symptomatic splenomegaly. Splenectomy has been used for over three decades as the initial treatment option (10,11,15,16). Splenectomy has been certainly beneficial for some patients resulting in a significant improvement of their pancytopenia. On the other hand splenectomy had no effect on bone marrow infiltrati-
on of HCs. As a result, approximately 50% of splenectomi-
zed patients had recurrent cytopenias that required systemic therapy. The introduction of interferon - alfa (IFN) in 1984 (22) and two new purine analogues, 2-deoxycoformycin (DCF) in 1984 (23) and 2-chloro-2-deoxyadenosine (2-CdA) in 1990 (24) in therapy of HCL dramatically improved treat-
ment option of HCL in the last years.

IFN has been shown to induce complete remission in 11% of patients (range 0% to 30%), DCF in 68.5% of pa-
tients (range 42% to 93%) and 2-CdA in 85% of patients (ran-
ge 75% to 91%) (14). IFN - alfa was the first drug in which the possibility to cure HCL was originally considered. The expectancy was not fulfilled. IFN - alpha was highly effecti-
ve in the management of HCL but did not eradicate and cure the disease. Relapses were observed after withdrawal of the therapy in all patients. DCF and 2-CdA were able to induce complete remission in the majority of the patients. The complete remission has been defined according to the criteria declared on the Third International Workshop on Hairy Cell Leukemia in 1990 (4) as complete absence of morphological evident HCs in the peripheral blood and bone marrow using routine light microscopy; normalization of peripheral blood cell counts and absence of palpable adenopathy and hepatosplenomegaly.

Nevertheless CR is often associated with finding of re-
sidual leukemic population (MRD) in the bone marrow if more sensitive immunohistochimical methods or PCR tech
tique to detect immunoglobulin heavy chain genes rearrangement are applied. The definition of MRD is diffi-
cult, because standardized criteria of MRD identification are lacking.

MRD has been observed in patients treated with IFN alfa (8), DCF (19, 24) and 2-CdA (1, 2, 7, 9, 12, 18, 26, 27) (tab.1). MRD was found in 13% (26) to 100% (2, 9, 13, 18, 24) of patients depending on the method used. Southern blot analysis (6) has been found not to be sensiti-
ve for detection of MRD.

The significance of MRD for early relapse and survival rate has to be established.
The posttherapy bone marrow sections were interpreted line the antibody is contributory to quantifying the extent of disease, particularly when HCs are interstitial and blended. This is done by using two antibodies: L26 (CD20) and MB2 (CD45RO) to evaluate core biopsies from 34 patients before and after therapy. Two remained positive by immunostaining alone, and one patient became negative by immunostaining. Detection of MRD: Hakimian et al. (12) used two B-lineage antibodies, L26 (anti CD20) and MB2 and T line antibody UCHL-1 (CD45RO) to evaluate core biopsies from 34 patients before and after therapy with 2-CdA. L26 (anti CD20) is a pan-B-cell antibody that is highly lineage specific. L26 (CD20) typically stains positive in 36% of HCL patients (13). UCHL-1 does not react with hairy cells. Five of 24 (21%) patients in CR by routine examination had MRD detected by immunostaining. Four of these 5 patients have been reevaluated at 1 year. One patient relapsed by routine examination, two remained positive by immunostaining alone, and one patient became negative by immunostaining. Hakimian et al. stress that immunostaining using the B-lineage antibody is contributory to quantifying the extent of disease, particularly when HCs are interstitial and blended with surrounding hematopoietic tissue, when HCs are present among fat cells in hypocellular marrow, when they are spindel-shaped, and when marrows are markedly fibrotic.

The posttherapy bone marrow sections were interpreted as positive for residual HCs if the following two criteria were met: 1. the L26 (CD20) - positive cells had the morphologic appearance of HCs, 2. the cells reacting with L26 (CD20) were more numerous than those reacting with UCHL-1 (CD45RO). Normally the Tcell are in bone marrow more numerous. When et al. (26) used the combination of two B-lineage antibodies anti CD20 and DBA.44 and one T-lineage antibody anti CD45RO (UCHL-1). They studied paraffin - embedded bone marrow core biopsies from 39 patients with HCL in CR for 3 months after a single cycle of 2-CdA and annually thereafter. MRD was detected in 5 of 39 (13%) patients. Two of the five patients (40%) with MRD at 3 months have relapsed, whereas only 2 of 27 (7%) positive with no MRD and at least one year of follow-up relapsed. They used nearly the same criteria as Hakimian et al. (12) defining MRD: The presence of CD20 or DBA.44 (B-cell) - positive cells in equal or greater numbers than CD45RO (T-cell) - positive cells and the presence of greater than 50% of the CD20 or DBA.44 positive cells exhibiting morphologic features consistent with HCs. As HCs were identified CD20- or DBA.44- positive biopsies with moderate to abundant cytoplasm and distinct cytoplasmic projections. CD20 demonstrated strong surface membrane positivity, whereas DBA.44 exhibited both cytoplasmic and surface membrane positivity. DBA.44 also outlines the cytoplasmic projections of hairy cells, however it tended to obscure the nuclear detail due to the intense cytoplasmic positivity.

Wehatoon et al. (26) admit that the used criteria may underestimate the true incidence of MRD, but they consider that they may detect a threshold of MRD that has clinical importance.

Ellison et al. (7) used as well the combination of L26 (CD20) and DBA.44 antibodies. Out of 154 bone marrow biopsies 50% exhibited staining with L26 and/or DBA.44 in five or more cells with morphologic features of hairy cells. HCs represented usually less than 1% of the total cellular population. In control bone marrow specimens DBA.44 stained only rare cells, fewer than one per highpowered field and usually only a few (less than 10) cells in entire biopsy. Because of the difficulties in identifying some L26 / DBA.44 - positive lymphocytes as either hairy cells or reactive lymphocytes, a bone marrow was considered contributory for residual hairy cells when five or more cells with both nuclear and cytoplasmic morphology features of hairy cells and with a characteristic pattern of staining with L26 and/or DBA.44 were positive. Ellison et al considered that some of the cases that had one to four HCs by immunohistochemical analysis were true positive. They observed HCL patients after 2-CdA therapy for up to 25 months after therapy. The amount of residual disease seemed to remain stable over a prolonged period of time in majority of patients.

Only DBA.44 antibody has been used by Houssine et al. (13). Bastie et al. (11) and Zak et al. (27).

Bastie et al. (11) defined MRD as <1% to 5% DBA.44 positive cells in bone marrow biopsies with no evidence of HCs by routine morphologic examination. At 6 months of 22 (36%) patients in CR had residual disease by immunostaining. Some observation not directly associated with the detection of MRD are noteworthy. First immunostaining with DBA.44 disclosed toprgrafic variations in HCL infiltrates in bone...tive disease was reflected by very low levels of sIL-2R which is considered as noninvasive marker of tumormass.

Falini et al. (8) used a panel of monoclonal antibodies directed against B-cell and hairy cell leukemia - associated antigens to identify residual HCs in bone marrow samples from 20 patients with HCL. They concluded that the best markers for identifying residual HCs in routine bone marrow biopsies were CD45RA (MAB 4KBS) and CD20 (MAB L26).

Matutes et al. (19) investigated the clinical significance and longterm followup of detecting MRD in HCL after treatment with DCF. MRD was assessed in 23 patients by immunophenotyping using a panel of antibodies : CD11c, CD25, CD103 and HCL which detect HCs. MRD had 10 of 23 (43%) patients. At a median followup of 72 months (range 15-105), 5 of 23 (22%) patients have relapsed with a median time of 59 months (range 15-105). MRD was detected in three of five patients who relapsed. MRD was defined in 7 of 18 who continued in clinical CR for a median of 80 months (range 6-98). There were no statistical differences in disease free survival between MRD+ and MRD- patients. This findings indicate that relapse after longterm remission achieved with DCF cannot be predicted when MRD is detected by sensitive methods. On the other hand, although differences in risk of relapse between patients with MRD+ or MRD- lack statisti- cal significance, there was a slight trend for a higher probability of relapse in patients with MRD+.

Excellent experience was shown with monoclonal antibody Bly7 (anti CD103) in HCL reported Thaler et al.(24). They investigated cryostat sections of bone marrow biopsies by an indirect immunoperoxidase technique. The strong reactive- ity of HCs with this marker was not altered after therapy with IFN-alpha2 and DCF six to forty six weeks after start of treatment. In this study, although differences in incidence of HCs by the MoAb Bly7 facilitates morphological identification of these cells. The typical cytoplasmic projections are clearly visible on the Bly7 stained cryostat sections. Normal bone marrow contains only a small number of Bly7 positive cells ranging from 0.0 to 1.0 % (mean 0.3%), whereas the percentage of cells recognized by pan-bcell markers is normally less than 1%. CD22 stains 0.7-3.0% (mean 1.7% of bone marrow cells). (24)

Residual HCs were detectable immunohistochemically with the MoAb Bly7 in all of the four patients in CR according to the morphological bone marrow examination and generally accepted criteria (4).

The high sensitivity of MoAb Bly7 has been confirmed by Konwalinka et al. (18). They detected MRD in 11 pa-
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Detection of MRD:

Hakimian et al. (12) used two B-lineage antibodies, L26 (anti CD20) and MB3, and T-lineage antibody UCHL-1 (CD45RO) to evaluate core biopsies from 34 patients before and after treatment with 2-CdA. L26 (anti CD20) is a pan-B-cell antibody that is highly lineage specific. L26 (CD20) typically stains positive in 81% of patients with HCL (13). UCHL-1 does not react with hairy cells. Five of 24 (21%) patients in CR by routine evaluation had MRD detected by immunostaining. Four of these 5 patients have been reevaluated at 1 year. One patient relapsed by routine evaluation, two remained positive by immunostaining alone, and one patient became negative by immunostaining.

Hakimian et al. stress that immunostaining using the B-lineage antibody is contributory to quantifying the extent of disease, particularly when HCs are interstitial and blended in normal marrow. When CD20 or other B-lineage antibodies alone or in combination with T-cell antibodies are used, the percentage of positive cells in the marrow has been significantly lower than when using the same antibodies in combination with anti-CD20 antibodies alone. Therefore, the use of antibodies in combination may be more sensitive in detecting residual disease.免疫

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Only DBA.44 antibody has been used by Hounieu et al. (13), Bastie et al. (1), and Zak et al. (27). Bastie et al. (1) defined MRD as 1% to 5% DBA.44 positive cells in bone marrow biopsies with no evidence of HCs by routine morphologic examination. At 6 months 8 of 22 (36%) patients in CR had residual disease by immunohistologic staining. The amount of residual disease seemed to remain stable over a prolonged period of time in majority of patients.

Hounieu et al. (13) defined MRD as 1% to 5% DBA.44 positive cells in bone marrow biopsies with no evidence of HCs by routine morphologic examination. At 6 months 8 of 22 (36%) patients in CR had residual disease by immunohistologic staining.

The high sensitivity of MoAb B-ly7 has been confirmed by Konwalinka et al. (18). They detected MRD in 11 patients with CR of HCL after 2-CdA therapy. At a follow-up period of 7-29 months (median 19.3 months) 9 of these patients with MRD at 3 months have relapsed, whereas only 2 of 27 (7%) with no MRD and at least one year of follow-up relapsed.

Excellent experiences with monoclonal antibody Bly7 (anti CD103) in HCL reported Thaler et al. (24). They investigated cryostat sections of bone marrow biopsies by immunohistochemical staining and generally accepted criteria. The characteristics of hairy cells include very low levels of sIL-2R which is considered as an invasive marker of tumor mass.

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tients remained in CR, whereas 2 patients relapsed 22 and 27 months after 2-CdA therapy.

To determine whether a flow-cytometric assay of bone marrow aspirates and peripheral blood cells is comparable with results obtained by immunostaining with B-ly7 in bone marrow biopsies, flow cytometric data were analysed obtained from patients 91 to 1046 days (median 345 days) after 2-CdA treatment. In 5 of 10 cases no HCs could be detected in bone marrow aspirates by using two-colour flow cytometry with B-ly7 and sTAMP3, however, immunostaining using B-ly7 still revealed HCs (ranging from 0.1 to 7.5%) in these cases. The presence of MRD after one course of 2-CdA was investigated by Filleul et al. (9) in 10 patients in CR at six months showed persistent evidence of detectable MRD without any sign of decrease over the observation period, in four patients for more than 12 months. Carbone et al. (2) got a positive PCR in all four patients in CR after a single 1-week course of continuous intravenous infusion of 0.1mg/kg/day of 2-CdA. Di Celle applied these in four patients Southern blot analysis of the IgH chain gene configuration and got germline configuration of IgH chain genes in all four patients suggesting CR without of MRD. Filleul et al. (9) got using Southern blot germline configuration in all 8 patients CR and shows that Southern blot techniques can detect at best 5% of leukemic cells, and the detection is even more difficult in HCL, because asparagine is frequently unsuccessful or may underestimate residual disease due to its focal nature.

We can conclude that methods sensitive for detecting MRD include immunostaining and Ig genes rearrangement studies using PCR. Immunohisto logic studies are more sensitive for detecting residual hairy cells than morphology alone. Despite the limitations, the PCR rearrangement analysis of immunoglobulin genes and Ig genes rearrangement may be the most sensitive. The results indicate that the amount of residual HCs seems to remain stable over a prolonged period of time in the majority of patients.

Conclusion

The true significance of MRD has to be established. A standardized technique for detection of MRD is needed. According to the literature, the PCR rearrangement analysis of immunoglobulin genes and Ig genes rearrangement may be the most sensitive. The results indicate that the amount of residual HCs seems to remain stable over a prolonged period of time in the majority of patients.

References

1. Busto JB, O’Regan MP, Pandolfo et al. Hairy cell leukaemia (HCL): phase II protocol for treatment of 21 patients with evaluable disease (UCLA). Br J Haematol 1998;101:78-9.
2. Carbone A, Ruiz G, Di Cella et al. Disease eradication in hairy cell leukaemia patients treated with 2-chloro-deoxyadenosine. Leukemia 1994;8:2019-21.
3. Caruso R, Baik S, Pannone W. Utilization of monoclonal antibody L26 in the identification and quantification of B cell lymphoma. Am J Pathol 1987;127:669-70.
4. Catovsky D, Gistl GW, Golomb HM. Meeting the report. The third international workshop on hairy cell leukaemia. Neoplasma 1999;46(10):781.
5. Catovsky D, Potter EF, Golomb DA et al. Lymphomatoid reticulosis (hairy cell leukaemia) a distinct clinicopathologic entity. Br J Haematol 1974;26:9-27.
6. De Celia P, Ruiz G, Rapaport D et al. Molecular evaluation of clonal expansion in hairy cell leukaemia patients treated with 2-chlorodeoxyadenosine. Leukemia Lymph 1994;11:110-24.
7. Ellison DL, Sharpe DW, Robbins BA et al. Immunophenotypic analysis of bone marrow biopsy after treatment for hairy cell leukaemia. Br J Haematol 1994;88:430-15.
8. Filleul L, Puech A, Plafig E et al. Selection of a panel of monoclonal antibodies for monitoring residual disease in peripheral blood and bone marrow in patients treated by hairy cell leukaemia. Blood 1999;94:378-84.
9. Filleul L, Delannoy A, Ferrart A et al. A single course of 2-chlorodeoxyadenosine does not eradicate leukaemic cells in hairy cell leukaemia patients in complete response. Leukemia 1998;12:1354.
10. Pandolfo G, Sigala F, Cattaneo S et al. Lymphomatoid reticulosis study de l’evolutio de 211 cas. Presse Med 1998;14:2799-0.
11. Golomb HM, Wadsworth RW. Response to splenectomy in 67 patients with hairy cell leukaemia: An evaluation of spleen weight and bone marrow involvement. Blood 1983;62:349-52.
12. Maksani D, Miotto M, Lorrain K et al. The significance of minimal residual disease in hairy cell leukaemia treated with 2-chlorodeoxyadenosine. Blood Cells Mol Dis 1993;21:455-62.
13. Martin J, Heman J, Rennet JA et al. Hairy cell leukaemia. Clinical features and effect of splenectomy. Scand J Haematol 1978;21:60-71.
14. Matutes E, Meeus D, McLennan K et al. The significance of minimal residual disease in hairy cell leukemia: An evaluation of spleen weight and bone marrow involvement. Blood 1993;82:1798-801.
15. Marini J, Schenb CW, van Zwet TL et al. Hairy cell leukaemia. A lympho cytic invasive. Br J Haematol 1974;26:9-27.
16. Matutes E, Meeus D, McLennan K et al. The significance of minimal residual disease in hairy cell leukemia: An evaluation of spleen weight and bone marrow involvement. Blood Cells Mol Dis 1993;21:455-62.
17. Jansen J, Hermans J, Remme J et al. Hairy cell leukemia. A B-lymphocytic leukaemia. J Clin Pathol 1984;2:1336-42.
18. Konwalinka G, Schirmer M, Hilbe W et al. Minimal residual disease in hairy-cell leukemia. Leukemia 1994;8:1253-6.
19. Matutes E, Meeus D, McLennan K et al. The significance of minimal residual disease in hairy cell leukemia: An evaluation of spleen weight and bone marrow involvement. Blood Cells Mol Dis 1993;21:455-62.
20. Martin J, Heman J, Rennet JA et al. Hairy cell leukaemia. Clinical features and effect of splenectomy. Scand J Haematol 1978;21:60-71.
21. Falini B, Pileri A, Fleghi L et al. Selection of a panel of monoclonal antibodies derived clonospecific probes. Leukemia 1990;4:1055.
22. Jansen J, Hermans J, Remme J et al. Hairy cell leukemia. A B-lymphocytic leukemia (hairy cell leukemia) a distinct clinicopathologic entity. Br J Haematol 1974;26:9-27.
23. Jansen J, Hermans J, Remme J et al. Hairy cell leukemia. A B-lymphocytic leukemia (hairy cell leukemia) a distinct clinicopathologic entity. Br J Haematol 1974;26:9-27.
24. Jansen J, Schutt HRE, van Zwet TL et al. Hairy cell leukemia. A B-lymphocytic leukemia (hairy cell leukemia) a distinct clinicopathologic entity. Br J Haematol 1974;26:9-27.
25. Visser L, Shaw A, Slupsky J et al. Monoclonal antibodies reactive with hairy cell leukemia: An evaluation of spleen weight and bone marrow involvement. Blood 1983;62:349-52.
26. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
27. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
28. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
29. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
30. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
31. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
32. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
33. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
34. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
35. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
36. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
37. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.
38. Wheaton S, Tallman MS, Hakimian D et al. Minimal residual disease may predict relapse with pentostatin (2’-deoxykoformicin). J Clin Oncol 1984;2:1336-42.