THALIDOMID IN IDIOPATHIC MYELOFIBROSIS

A STATUS REPORT

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Introduction

Idiopathic myelofibrosis is characterized by progressive accumulation of connective tissue in the bone marrow which is accompanied by extramedullary haematopoiesis with enlargement of the spleen and liver (1-8). The clinical course is chronic in the large majority of patients, although a subgroup is characterised by a rapidly lethal course with death within a few months from diagnosis (= acute myelofibrosis) (5,8,9). In recent years it has become clear that the classical clinical phenotype of IMF as described above is preceded by a prefibrotic stage , which clinically may mimick essential thrombocytosis (10,11). Besides bone marrow fibrosis IMF is featured by a marked angiogenesis in the bone marrow and spleen. Indeed, neovascularisation of the bone marrow has been described many years ago as highly characteristic of idiopathic myelofibrosis (12,13) being most pronounced in patients with osteomyelosclerosis but present in the other chronic myeloproliferative disorders as well (12-19). These stromal changes are considered to develop consequent to the release of various growth factors from rapidly proliferating, large and dysplastic megakaryocytes always located in clusters near to sinusoids (20-28). These growth factors include among others platelet-derived growth (PDGF),basic fibroblast growth factor (bFGF) ,vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-beta) , which are mitogenic for fibroblast and/or endothelial proliferation. Concerning VEGF elevated levels of this growth have also been found in a high proportion of patients with IMF (29-32).

The treatment of idiopathic myelofibrosis aims at reducing the hypermetabolic symptoms associated with clonal myeloproliferation/myeloaccumulation and myeloid metaplasia (1-3,5,7). Conventionally these patients have been treated with busulphan or hydroxyurea. Both drugs are potentially leukemogenic – at least when being used sequentially in this patient group (33). In younger patients alpha-interferon or PEG-Intron may be useful alternatives (34,35). Besides treatment with iron, folic acid and vitamin B12, anemia in IMF may be corrected by treatment with recombinant human erythropoetin, danazol or prednisolone (2,3,5,36-38). In recent years several novel treatment modalities have been tried (38,39). Considering the pronounced angiogenesis in the bone marrow and spleen and the potential pathogenetic role of VEGF treatment with thalidomide – either as monotherapy or as combinational therapy with prednisolone – has been used in these patients (40-55). Low-dose Thalidomide + prednisolone appears to be highly successful in correcting anemia with a response rate of about 50-60 % . However, in only a subgroup of patients a regression of spleen size is recorded . As one of the deliverables in WP9. CMPD this report

summarizes the results obtained in clinical trials on thalidomide in IMF, and presents proposals for future trials with thalidomide/ thalidomide analoges in combination with other agents based upon their potential mechanisms of action.

Studies on Thalidomide in Idiopathic Myelofibrosis

Several studies dealing with the efficacy and safety of thalidomide in IMF have shown that some patients benefit from treatment with thalidomide as evidenced by an increase in the Hb-concentration and a decrease in spleen size (40- 55). The treatment is very often associated with significant side effects in particular when using doses above 100-200 mg, whereas low-dose thalidomide (50mg/day) in combination with prednisolone seems to be associated with far less side effects but still highly effective with an increase in the HB-concentration in about 60 % of the patients (48,53,). However, there is still a need to minimize non-haematologic toxicity associated with thalidomide therapy . In this context the novel thalidomide analoges seem very promising (56-58).

Thalidomide Analoges

CC-5013 (Lenalidomide; Revlimid) is an immunomodulatory analog of thalidomide that is substantially more potent than the parent drug in terms of both anti-angiogenic and anti-TNF-alpha activity. The compound has also significantly fewer non-haematologic toxicities and has shown very promising results in both multiple myeloma (59,60), the myelodysplastic syndrome (61) as well as in idiopathic myelofibrosis (62).

Discussion and Conclusion : Bases upon the very promising results from studies on low-dose thalidomide and prednisolone in IMF a randomised **s**tudy of a large series of patients is needed to clarify if combinational therapy with Revlimid + glucocortocoids are superior to Revlimid and glucocorticoid monotherapy (dexamethasone (Dex) (40 mg daily on days 1-4 and days 14- 17 every month for six months). Combinational therapy with other novel potent antiangiogenic agents (eg. Bevacizumab (63-66), bortezomib (67-76) , arsenic trioxide (77-80), histon deacetylase inhibitors (81-87) , PTK787 (88-93), zoledronic acid (94-97) is relevant to consider in ensuing studies to target simultaneously multiple aberrant signal transduction pathways responsible for the enhanced myeloproliferation , decreased apoptosis (myeloaccumulation) and the marked endothelial proliferation in idiopathic myelofibrosis.

References

1. Tefferi A. The Chronic Myeloproliferative Disorders. Semin Hematol 1999; 36(Supp2):3-8.
2. Reilly JT. Idiopathic myelofibrosis: pathogenesis, natural history and management. Blood Rev 1997; 11(4): 233-42
3. Tefferi A. Myelofibrosis with myeloid metaplasia N Engl J Med 2000; 342(17):1255-65.
4. Spivak JL. The chronic myeloproliferative disorders.: clonality and clinical heterogeneity. Semin Hematol 2004; Apr 41(2 Suppl 3) : 1-5.
5. Fruchtman SM. Treatment paradigms in the management of chronic myeloproliferative disorders. Semin Hematol 2004; Apr; 41(2 Supp 3): 18-22.
6. Ward HP & Block MH. The natural history of agnogenic myeloid metaplasia (AMM) and a critical evaluation of its relationship with the myeloproliferative syndrome. Medicine (Baltimore) 1971; 50: 357.
7. Reilly JT. Idiopathic myelofibrosis: pathogenesis, natural history and management. Blood Rev 1997; 11(4): 233-42
8. Hasselbalch HC. Idiopathic myelofibrosis. Am J Hematol 1990; 34:291-300.
9. Cervantes F, Pereira A, Esteve J, Rafel M, Cobo F, Rozman C & Montserrat E. Identification of "short-lived" and "long-lived" patients at presentation of idiopathic myelofibrosis. Br J Haematol 1997; 97: 635-640.
10. Thiele J , Zankovich R, Steinberg T, Kremer B, Fischer R, Diehl V. Primary (essential) thrombocyhemia versus initial (hyperplastic) stages of agnogenic myeloid metaplasia with thrombocytosis. A critical evaluation of clinical and histomorphological data. Acta Haematol 1989; 81:192-202.
11. Thiele J, Kvasnicka HM, Fischer R, Diehl V. Clinicopathological impact of the interaction between megakaryocytes and myeloid stroma in chronic myeloproliferative disorders: a concise update. Leuk Lymphoma 1997; 24: 463-81.
12. Burkhardt R,Bartl , Beil E, Demmler K, Hoffman E, Kronseder A: Myelofibrosis-Osteomyelosclerosis Syndrome- Review of Literature and Histomorphology. In: " Advances in the Biosciences , Dahlem Workshop on Myelofibrosis-Osteomyelosclerosis Syndrome". Berlin Nov 13-15, 1974; 16:9-56.
13. Reilly JT, Nash JR, Mackie MJ, McVerry BA. Endothelial cell proliferation in myelofibrosis. Br J Haematol 1985; 60(4):625-30.
14. Lisse I, Hasselbalch H , Junker P. Bone marrow stroma in idiopathic myelofibrosis and related diseases. An immunohistochemical study. APMIS 1991; 99:1171-78.
15. Thiele J, Rompcik V, Wagner S, Fischer R. Vascular architecture and collagen type IV in primary myelofibrosis and polycythaemia vera.: An immunomorphomeric study on trephine biopsies of bone marrow. Br J Haematol 1992; 80(2): 227-34.
16. Thiele J, Kvasnicka HM, Fischer R, Diehl V. Clinicopathological impact of the interaction between megakaryocytes and myeloid stroma in chronic myeloproliferative disorders: a concise update. Leuk Lymphoma 1997; 24: 463-81.
17. Lundberg LG, Lerner R, Sundelin R, Rogers R, Folkman J, Palmblad J. Bone marrow in polycythemia vera , chronic myelocytic leukemia and myelofibrosis has an increased vascularity. Am J Pathol 2000; 157(1):15-9.

18. Panteli K, Zagorianakou N, Bai M, Katsaraki A, Agnantis NJ, Bourantas K. Angiogenesis in chronic myeloproliferative diseases detected by CD34 expression. Eur J Haematol 2004; 72(6): 410-5.
19. Barosi G, Vittorio R, Margherita M, Luca VG, Alessandro P, Vittorio N, Isabella R, Rita C, Monia M, Mario B, Umberto M. Spleen neoangiogenesis in patients with myelofibrosis with myeloid metaplasia. Br J Haematol 2004; 124(5):618-25.
20. Castro-Malaspina H. Pathogenesis of myelofibrosis: role of ineffective megakaryopoiesis and megakaryocyte components. In : Myelofibrosis and the Biology of Connective Tissue.1984: 427-454.
21. ReillyJT, Barnett D, Dolan G, Forrest P, Eastham J, Smith A. Characterization of an acute micromegakaryocytic leukaemia – evidence for the pathogenesis of myelofibrosis. Br J Haematol 1993; 83(1):58-62.
22. Martyre MC, Magdelenat H, Bryckaert H, Laine – Bidron C & Calvo F. Increased intraplatelet levels of platelet-derived growth factor and transforming growth factor-b in patients with myelofibrosis with myeloid ,metaplasia. Br J Haematol 1991; 77:80-86.
23. Martyre MC, Romquin N, Le Bousse-Kerdiles MC, Chevillard S, Benyahia B, Dupriez B, Demory JL, & Bauters F. Transforming growth factor –beta and megakaryocytes in the pathogenesis of idiopathic myelofibrosis. Br J Haematol 1994; 88:9-16.
24. Martyre MC, Le Bousse-Kerdiles MC ,Romquin N, , Chevillard S, Praloran V,, Demory JL, & Dupriez B. Elevated levels of basic fibroblast growth factor in megakaryocytes and platelets from patients with idiopathic myelofibrosis. Br J Haematol 1997; 97::441-448.
25. Marie-Caroline Le Bousse-Kerdiles, Sylvie Chevillard, Agnes Charpentier, Nicole Romquin, Denis Clay, Florence Smadja-Joffe, Vincent Praloran, Brigitte Dupriez, Jean – Loup Demory, Claude Jasmin, Marie-Claire Martyre. Differential expression of transforming growth factor-beta, basic fibroblast growth factor, and their receptors in CD34+ hematopoietic progenitor cells from patients with myelofibrosis and myeloid metaplasia. Blood 1996; 88(12): 4534-4546.
26. Le Bousse-Kerdiles MC,Martyre MC. Dual implication of fibrogenic cytokines in the pathogenesis of fibrosis and myeloproliferation in myeloid metaplasia with myelofibrosis. Ann Hematol 1999 78:437-44.
27. Posee PL, Willer A, Weisser A, Kuhn C, Kreil S, Paschka P, Saussele S, Hehlmann R, Hochhaus . Increased levels of bFGF mRNAtranscripts in Ph negative chronic myeloproliferative disorders but not in chronic myelogenous leukemia. Blood 2000; 96(11):745a, Abstract # 3221.
28. Hasselbalch HC. Idiopathic Myelofibrosis. Clinical Aspects and Studies on Extracellular Matrix Metabolism. Thesis . Danish Med Bulletin 1993; 40:39.
29. Raimundo FD, Azzaro MP, Palumbo GA, Bagnoto S, Stagno F, Giustolisi GM, Cacciola E, Sortino G, Guglielmo P, Giustolisi R. Elevated vascular endothelial growth factor (VEGF) serum levels in idiopathic myelofibrosis. Leukemia 2001; 15: 976-980.
30. Raimondo FD, Palumbo GA, Molica S, Giustolisi R. Angiogenesis in chronic myeloproliferative diseases. Acta Haematol 2001; 106:177-183.
31. Murphy P, Ahmed N, Hassan HT. Increased serum levels of vascular endothelial growth facor correlate with slenomegaly in polycythemia vera. Leuk Res 2002 ; 26(11):1007-1010.

32. Musolino C, Calabro' L, Bellomo G, Martello F, Loteta B, Pezzano C, Rizzo V, Alonci A. Soluble angiogenic factors:implications for chronic myeloproliferative disorders. Am J Hematol 2002; 69(3):159-63.
33. Nielsen I, Hasselbalch HC. Acute Leukemia and myelodysplasia in patients with Philadelphia chromosome negative chronic myeloproliferative disorder treated with hydroxyurea alone or with hydroxyurea after busulphan. Am J Hematol 2003; 74(1): 26-31.
34. Bachleitner-Hofmann T, Gisslinger H. The role of interferon-alpha in the treatment of idiopathic myelofibrosis. Ann Hematol 1999; 78(12):533-8.
35. Radin AI, Kim HT, Grant BW, Bennett JM, Kirkwood JM, Stewart JA, Hahn RG, Dutcher JP, Wiernik PH, Oken MM. Phase II study of alpha2 interferon in the treatment of the chronic myeloproliferative disorders. Cancer 2003; 98(1):100-9.
36. Hasselbalch HC, Clausen NT, Jensen BA. Successful treatment of anemia in idiopathic myelofibrosis with recombinant human erythropoietin. Am J Hematol 2002; 70(2):92-9.
37. Cervantes F, Alvarez-Larran A, Hernandez-Boluda JC, Sureda A, Torrebadell M, Montserrat E. Erythropoietin treatment of the anaemia of myelofibrosis with myeloid metaplasia: results in 20 patients and review of the literature. Br J Haematol 2004; 127(4):399-403.
38. Hennessy BT, Thomas DA, Giles FJ, Kantarjian H, Verstovsek S. New approaches in the treatment of myelofibrosis. Cancer 2004 Nov 24 (Epub ahead of print).
39. Cervantes F. Modern management of myelofibrosis. Br J Haematol 2005 (OnlineEarly)
40. Barosi G, Grossi A, Commoti B et al. Safety and efficacy of thalidomide in patients with myelofibrosis and myeloid metaplasia. Br J Haematol 2001; 114: 78-83.
41. Canepa L, Balerini F, Varaldo R , Quintino S, Clavio LRM, Miglino M, Pierri I, Gobbi M. Thalidomide in agnogenic and secondary myelofibrosis. Br J Haematol 2001; 115: 313-315.
42. Pozzato G, Zorat F, Nascimben F, Comar C, Kikic F, Festini G. Thalidomide in compensated and decompensated myelofibrosis with myeloid metaplasia. Haematologica 2001 86(7): 772-3.
43. Elliot MA, Mesa RA, Li C-Y et al. Thalidomide treatment in myelofibrosis with myeloid metaplasia. Br J Haematol 2002; 117: 288-296.
44. Piccaluga PP, Visani G, Pileri SA et al. Clinical efficacy and antiangiogenic activity of thalidomide in myelofibrosis with myeloid metaplasia: a pilot study.Leukemia 2002; 16: 1609-1614.
45. Merup M, Kutti J, Birgergard G, Mauritzson N, Bjrkholm M, Markevarn B, Maim C, Westin J, Palmblad J. Med Oncol 2002; 19(2):79-86.
46. Barosi G, Michelle E, Letizia C, Fillipo B, Paulo PP, Giuseppe V, Monia M, Gabriele P, Francesca Z, Tefferi A. Thalidomide in myelofibrosis with myeloid metaplasia : a pooled analysis of individual patient data from five studies. Leuk Lymphoma 2002; 43(12): 2301-7.
47. Bonn D. Thalidomide: no benefit in myelofibrosis with myeloid metaplasia. Lancet Oncol 2003; 4(2): 70.
48. Mesa RA, Steensma DP, Pardanani A, Li CY, Elliot M, Kaufmann SH, Wiseman G, Gray LA, Schroeder G, Reeder T, Zeldis JB, Tefferi A. A phase 2 trial of combination low-dose thalidomide and prednisolone for the treatment of myelofibrosis with myeloid metaplasia. Blood 2003; 101(7): 2534-41.
49. Tefferi A. Treatment approaches in myelofibrosis with myeloid metaplasia: the old and the new. Seminar Hematol 2003; 40(1 Suppl 1): 18-21.

50. Matthews SJ, McCoy. Thalidomide: a review of approved and investigational uses. Clin Ther 2003; 25(2):342-95.
51. Visani G, Mele A, Malagola M, Isidori A, Finelli C, iccaluga PP. Sequential combination of thalidomide and erythropoietin determines transfusion independence and disease control in idiopathic myelofibrosis previously insensitive to both drugs used as single agents. Leukemia 2003; 17(8):1669-70.
52. Eleutherkis-Papaiakovou V, Bamias A, Dimopoulos MA. Thalidomide in cancer medicine. Ann Oncol 2004; 15(8): 1151-60.
53. Marchetti M, Barosi G, Balestri F, Viarengo G, Gentili S, Barulli S, Demory JL, Ilariucci F, Volpe A, Bordessoule D, Grossi A, Le Bousse-Kerdiles MC, Caenazzo A, Pecci A, Falcone A, Broccia G, Bendotti C, Bauduer F, Buccisano F, Dupriez B. Low-dose thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia : a Phase II trial. J Clin Oncol 2004; 22(3): 424-31.
54. Strupp C, Germing U, Scherer A, Kundgen A, Modder U, Gatterman N, Haas R. Thalidomide for the treatment of idiopathic myelofibrosis. Eur J Haematol 2004; 72(1): 52-7.
55. Kumar S, Witzig TE, Raykumar SV. Thalidomide: Current role in the treatment of non-plasma cell malignancies. J Clin Oncol 2004; 22: 2477-2488.
56. Dredge K, Dalgleish AG, Marriot JB. Thalidomide analogs as emerging anti-cancer drugs. Anticancer Drugs 2003; 14(5):331-5.
57. Mitsiades CS, Mitsiades N. CC-5013 (Celgene). Curr Opin Investig Drugs 2004; 5(6): 635-47.
58. Galustian C, Labarthe MC, Bartlett JB, Dalgleish AG. Thalidomide-derived immunomodulatory drugs as therapeutic agents. Expert Opin Biol Ther 2004; 4(12): 1963-1970.
59. Richardson PG, Schlossman RL, Weller E, Hideshima T, Mitsiades C, Davies F, LeBlanc R, Catley LP, Doss D, Kelly K, McKenney M, Mechlowicz J, Freeman A, Deocampo R, Rich R, Ryoo JJ, Chauhan D, Balinski K, Zeldis J, Anderson KC. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 2002; 100(9):3063-7.
60. Rajkumar SV, Hayman SR, Lacy MQ, Dispenzieri A, Hoering A, Geyer SM, Zeidenrust SR, Greipp PR, Fonseca R, Lust JA, Russell SJ, Kyle RA, Witzig TE, Gertz MA. Combination therapy with CC-5013 (Lenalidomide;Revlimid) plus dexamethasone for newly diagnosed myeloma (MM). Blood 2004; 104(11): Abstract # 331.
61. List AF, Kurtin SE, Glinsman-Gibson BJ et al. Efficacy of CC5013 in myelodysplastic syndromes(MDS). N Engl J Med 2004 (in Press).
62. Tefferi A, Hogan WJ, Wolanskyj AP, Shah TA, Reyes GE, Hoering A, McClure RF, Mesa RA. A Phase II study of CC-5013 treatment for myelofibrosis with myeloid metaplasia. Blood 2004; 104(11): Abstract # 1505.
63. Sharieff W. Bevacizumab in colorectal cancer. N Engl J Med 350(23):2335-42.
64. Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. J Clin Onco 2004; Nov 8 (Epub ahead of print).
65. Gotlib J, Jamieson CHM, List A, Cortes J, Albitar M, Sridhar K, Dugan K, Qesada S, Diaz G, Pate O, Novotny W, Chen H, Greenberg PL. Phase II study of bevacizumab (anti-VEGF

humanized monoclonal antibody) in patients with myelodysplastic syndrome (MDS): Preliminary results. Blood 2003; 102: 425a

1. Karp JE, Gojo I, Pili R, Gocke CD, Greer J, Guo C, Qian D, Morris L, Tidwel M, Chen H, Zwiebel J. Targeting vascular endothelial growth facor for relapsed and refractory adult acute myelogenous leukemias: Therapy with sequential 1-beta-D-arabinofuranosylcytosine, mitoxantrone and bevacizumab. Clin Cancer Res 2004; 10:3577-3585.
1. Hideshima T et al. NF-kB as a therapeutic target in multiple myeloma . J Biol Chem 2002; 277: 16639-16647).
1. Mitsiades N et al. Molecular sequelae of proteosome inhibition in human multiple myeloma cells. Proc Natl Acad Sci USA 2002; 99:14374-14379.
1. Hideshima T et al. Molecular mechanism mediating antimyeloma activity of proteosome inhibitor PS-341. Blood 2003: 101; 1530-1534.).
1. Adams J, Palombella VJ, Elliot PJ, et al. Proteosome inhibitors : a novel class of potent and effective antitumor agens. Cancer Res 1999;59: 2615-22.
1. Adams J, Palombella VJ, Elliot PJ. Proteasome inhibition.: a new strategy in cancer treatment. Invest New Drugs 2000; 18:109-21).
1. Hideshima T et al. The proteosome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res 2001; 61: 3071-3076.
1. Richardson PG et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003; 348: 2609-2617).
1. Hollmig K, Stover J, Talamo G, Fassas A, Lee C, Anaissie E, Tricot G, Barloigie B. Bortezomib (Velcade) + adrimycin + Thalidomide + Dexamethasone (VATD) as an effective regimen in patients with refractory or relapsed multiple myeloma. Blood 2004;104(11): abstract # 2399).
1. Orlowski RZ et al. Phase I trial of the proteosome inhibitor PS-341 in patients with refractory hematologic malignancies. J Clin Oncol 2002; 20: 4420-4427.
1. Cortes J, Thomas D, Koller C, Giles F, Estey E, Faderl S, Garcia-Manero G, McConkey D, Patel G, Guerciolini R, Wright J, Kantarjian H. Phase I study of bortezomib in refractory or relapsed acute leukemias. Clini Cancer Res 2004; 10:3371-3376.
1. List A, Beran M, DiPersio J, Slack J, Vey N, Rosenfeld CS, Greenberg P. Opportunities for Trisenox (arsenic trioxide) in the treatment of myelodysplastic syndromes. Leukemia 2003; 17(8): 1499-507.
1. Evens AM, Tallman MS, Gartenhaus RB. The potential of arsenic trioxide in the treatment of malignant disease: past, present, and future. Leuk Res 2004; 28(9):891-900.

79. Vey N. Arsenic trioxide for the treatment of myelodysplastc syndromes. Expert Opin Pharmacother 2004; 5(3): 613-21.
80. Raza A, Buonamici S, Lisak L, Tahir S, Li D, Imran M, Chaudary NI, Pervaiz H, Gallegos JA, Alvi MI, Mumtaz M, Gezer S, Venugopal P, Reddy P, Galili N, Candoni A, Singer J, Nucifora G. Arsenic trioxide and thalidomide combination produces multi-lineage haematological responses in myelodysplastic syndromes patients, particularly in those with high pre-therapy EVI1 expression. Leuk Res 2004 28(8): 791-803.

81. Marks PA, Richson VM, Rifkind RA. Histone deacetylase inhibitors: inducers of differentiation or apoptosis of transformed cells. J Natl Cancer Inst 2000; 92: 1210-6.

82. Johnstone RW. Histone-deacetylase inhibitors: novel drugs fro the treatment of cancer. Nat Rev Drug Disc 2002; 1:287-99.
83. Catley L, Weisberg E, Tai Y, Atadja P, Remiszewski S, Hideshima T, Mitsiades N, Shringapure R, LeBlanc R, Chauhan D, Munshi NC, Schlossman R, Richardson P, Griffin J, Anderson KC. NVP-LAQ824 is a potent novel histone deacetylase inhibitor with significant activity against multiple myeloma. Blood 2003; 102: 2615-2622.
84. Atadja P, Gao L, Kwon P, Trogani N, Walker H, Hsu M, Yeleswarapu L, Chandramouli N, Prez L, Versace R, Wu A, Sambucetti L, Lassota P, Cohen D, Bair K, Wood A, Remiszewski R. Selective growth inhibition of tumor cells by a novel histone deacetylase inhibitor, NVP-LAQ824. Cancer Research 2004; 64: 689-695.
85. Deroanne CF, Bonjean K, Servotte S et al. Histone deacetylases inhibitors as anti-angiogenic agents altering vascular endothelial growth factor signaling. Oncogene 2002; 21: 427-36.
86. Rossig L, Li H, Fisslthaler B et al. Inhibitors of histone deacetylation downregulate the expression of endothelial nitric oxide synthase and compromise endothelial cell function in vasorelaxation and angiogenesis. Circ Res 2002; 91: 837-44.
87. Qian DZ, Wang X, Kachhap SK, Kato Y, Wie Y, Zhang L, Atadja P, Pili R. The histone deacetylase inhibitor NVP-LAQ824 inhibits angiogenesis and has a greater antitumor effect in combination with the vascular endothelial growth facor receptor tyrosine kinase inhibitor PTK787/ZK222584. Cancer Research 2004; 64: 6626-34.
88. J Traxler P, Bold G, Buchdunger E, Caravatti G, Furet P, Manley P et al. Tyrosine kinase inhibitors : from rational design to clinical trials. Med Res Rev 2001; 21: 499-512.
1. Wood JM, Bold G, Buchdunger E, Corzens R, Ferrai S, Frei J et al. PTK787/ZK222584/ZK222584 , a novel and potent onhibitor f vascular endothelial growth factor-induced responses and tumour growth after oral administration. Cancer Res 2000; 60: 2178-89.
90. Drevs J, Muller-Driver R, Wittig C, Fuxius S, Esser N, Hugenschmidt H et al. Effects of PTK787/ZK222584/ZK222584, a specific inhibitor of vascular endothelial growth factor receptor tyrosine kinases, on primary tumour, metastasis, vessel density, and blood flow in a murine renal cell carcinoma model. Cancer Res 2000; 60: 4819-24.
91. Thomas AL, Morgan B, Drevs J et al.Vascular endothelial growth factor receptor tyrosine kinase inhibitors: PTK787/ZK222584. Semin Oncol 2003; 30:32-8.
92. Morgan B, Thomas AL, Drevs J et al. Dynamic contrast-enhanced magnetic resonance imaging asa biomarker for the pharacological response to PTK787/ZK222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases , in patients with advanced colorectal cancer and liver metastasis: results from two phase I studies. J Clin Oncol 2003; 21: 3955-64.
93. List AF, Giles F, Rae PE, Dugan M, Greenberg J, Osama S, Schuster MW, Laurent D, Feldman EJ. Phase I trial of PTK787/ZK 222584 , an inhibitor of vascular endothelial growth factor receptor tyrosine kinases, in acute myeloid leukaemia and myelodysplastic syndrome. Blood 2002; 100(11); abstract # 13 08.

94. Santini D, Vincenzi B, Avvisati G et al. Pamidronate induces modifications of circulating angiogenic factors in cancer patients. Clin Cancer Res 2002; 8:1080-1084.
95. Chuah C, Tipping AJ, Goldman JM, Melo JV. Zoledronate is active against imatinib mesylate-resistant chronic myeloid leukaemia cell lines and synergistic/additive when combined with imatinib mesylate. Blood 2003; 19a. Abstract 57.
96. Kuroda J, Kimura S, Segawa H, Ottmann OG, Maekawa T. The anti-leukemic effects of third-generation biphosphonate, zoledronic acid. Blood 2003; 596a, abstract 219.
97. Kimura S, Kuroda J, Segawa H, Sato K, Nogawa M, Yasa T, Ottmann OG, Maekawa T. Antiproliferative efficacy of the third-generation biphosphonate , zoledronic acid , combined with other anticancer drugs in leukaemic cell lines. Int J Hematol 2004; 79(1):37-43.