Drugs of the Future 2007, 32(1): 45-50

CCC: 0377-8282/2007
DOI: 10.1358/dof.2007.032.01.1052960

Review Article

Combination therapy with valproic acid in cancer: initial clinical approach

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CONTENTS

Abstract

Valproic acid is well established as an anticonvulsant and mood-stabilizing drug. However, its ability to inhibit histone deacetylases (HDACs) at therapeutic concentrations has led to its investigation in the reactivation of dormant tumor suppressor genes and its potential in the treatment of cancer. Preclinical studies have provided evidence for its efficacy in a number of human cancers, including breast, endometrial and prostate cancer, and in the treatment of acute myeloid leukemia (AML). Early clinical studies in hematological cancers have shown promising efficacy in combination with the demethylating agent *all-trans*-retinoic acid (ATRA) in AML and myelodysplastic syndromes (MDS). A number of studies are ongoing, including a phase III study with standard induction and consolidation therapy in up to 500 older patients with newly diagnosed AML. Promising evidence of efficacy has also been demonstrated in patients with solid tumors, including breast cancer and melanoma, and ongoing studies are evaluating valproic acid in the treatment of glioblastoma and non-small cell lung cancer (NSCLC).

Introduction

Valproic acid is a short-chain branched fatty acid that is well established as an anticonvulsant and mood-stabilizing drug, principally in the treatment of epilepsy and bipolar disorder. It has, however, recently been shown to inhibit histone deacetylases (HDACs) at therapeutic concentrations (1-3). HDACs are involved in epigenetic events via histone modification. This modification of key histone amino acids, in addition to genetic changes, has been identified as a key mechanism in the silencing of tumor suppressor genes that leads to the development of carcinogenesis (Fig. 1). The impact of epigenetic changes on chromatin structure and gene transcription patterns and the role of HDAC inhibitors in the reactivation of dormant tumor suppressor genes have been a focus of research in the development of novel strategies for the treatment of cancer (4, 5).

Evidence from preclinical studies

A body of evidence has demonstrated the potential activity of valproic acid in a number of human cancers. The HDAC-inhibitory activity of valproic acid was investigated in the context of a prototypical epigenetically silenced tumor suppressor gene, retinoic acid receptor β2 (RARβ2), in human breast cancer cells. In combination with retinoic acid and the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine (decitabine), valproic acid increased histone acetylation at the silenced RARβ2 promoter of MCF7 human breast cancer cells. The combination also inhibited the proliferation of both estrogen receptor ERα-positive and ERα-negative breast cancer cell lines (6).

In six endometrial cancer cell lines, valproic acid was shown to inhibit cell growth, induce cell cycle arrest and apoptosis, and inhibit the expression of genes related to the malignant phenotype. The antitumor effect of valproic acid was demonstrated in nude mice transplanted with human endometrial tumor HEC-1B cells and treated with valproic acid for 5 weeks. All the treatment groups had statistically significantly smaller tumors than the control groups and tumor weights in the treatment groups were 75% less than those in the control cohort (7). However, in an *in vitro* model using human endometrial adenocarcinoma cells, valproic acid significantly enhanced the proliferative activity of 17β-estradiol. In this study, similar effects of valproic acid on cell proliferation were also observed in the ER-positive MCF7 breast cancer cell line. These results indicate that the identification of responsive tumor types is vital, as valproic acid may enhance the growth of ER-positive malignancies (8).

Valproic acid stimulated the differentiation of transformed hematopoietic progenitor cells and leukemic blasts from acute myeloid leukemia (AML) patients (1). In another study, valproic acid stimulated the proliferation, but not the differentiation, of human $CD34^+$ hematopoiet-

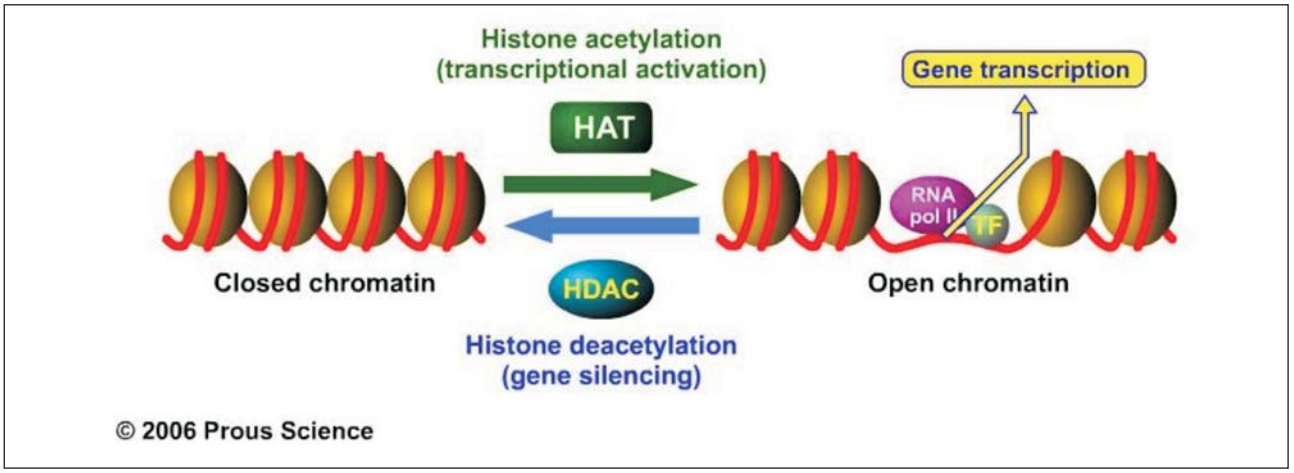

Fig. 1. A simplified model of transcriptional regulation. Histone acetylation (HAT) of histones weakens histone-DNA interactions, leading to a destabilization of nucleosome structure (open chromatin) that allows transcription factors (TF) and RNA polymerase to access their DNA targets. Histone deacetylase (HDAC) antagonizes this process by removing the acetyl group of histones, which leads to a closed chromatin configuration.

ic stem cells. It also increased the self-renewal potential of murine hematopoietic stem cells. These properties indicated that treatment with valproic acid in combination with conventional chemotherapy could have potential in the treatment of AML by stimulating the entry of quiescent hematopoietic and leukemic stem cells into the cell cycle (9).

A recent study using AML cells showed that valproic acid, as well as other HDAC inhibitors, potentiated *all-trans*-retinoic acid (ATRA) induction of folate receptor-β (FR-β) gene transcription and FR-β mRNA/protein expression in leukemic cells. FR-β is a protein expressed in about 70% of AMLs, which is capable of binding and internalizing folic acid and its γ-carboxyl conjugates and antifolates. Therefore, the combination of ATRA and HDAC inhibitors, including valproic acid, could facilitate selective FR-β-targeted therapies for AML (10).

In addition, valproic acid strongly inhibited the proliferation of human and rat glioma cells *in vitro* (11), and induced apoptosis and cell cycle arrest in poorly differentiated thyroid cancer cells at concentrations slightly higher than the therapeutic levels for the treatment of epilepsy (12). Valproic acid was also shown to promote re-differentiation of poorly differentiated thyroid cancer cells, thus restoring their ability to capture and concentrate iodine (13). These properties indicate that valproic acid might have a dual mechanism of action in the treatment of this cancer. A recent study in androgen receptor-positive (LNCaP, C4-2) and androgen receptor-negative (DU 145, PC-3) prostate cancer cell lines showed that chronic treatment with valproic acid resulted in a marked decrease in proliferation of prostate cancer cells *in vitro* and a significant reduction of tumor xenograft growth *in vivo*. Decreases in net proliferation rate were correlated with increased caspase-2 and caspase-3 activation, independent of androgen regulation (14).

Further evidence from recent studies using a panel of cancer cell lines, including breast adenocarcinoma, sarcoma and colon carcinoma, showed that valproic acid had a strong inhibitory effect against all seven cell lines tested. The ability of valproic acid in combination with a DNA methylation inhibitor to potentiate the antitumor activity of cytotoxic agents was also shown in a nude mouse HT-1080 fibrosarcoma xenograft model. In animals treated with doxorubicin for 3 weeks, with or without hydralazine plus valproic acid, tumors disappeared at day 21. Moreover, in animals treated with doxorubicin alone there was a rapid tumor re-growth, whereas animals treated with the combination remained tumor-free. This finding may be relevant for patients who have minimal residual disease after curative attempts by surgery, chemotherapy and/or radiotherapy. The combination treatment also led to an increase in the cytotoxicity of gemcitabine, cisplatin and doxorubicin in HeLa cervical cancer cells (15).

Clinical studies

Two dose-finding studies were conducted with valproic acid alone. The histone acetylation-inducing and HDAC-inhibitory activity of valproic acid was demonstrated in 12 newly diagnosed patients with cervical cancer. Histone H3 and H4 hyperacetylation in tumor samples was observed in most patients treated with magnesium valproate 20-40 mg/kg for 5 days. No grade 3 toxicity was observed, but 9 patients had grade 2 depressed consciousness (16). A dose-escalating phase I study was performed in 26 patients with pretreated and progressive malignant disease. Patients were treated with valproic acid 30, 60, 75, 90 and 120 mg/kg/day by infusion for 5 days, with the treatment repeated after a 2-week interval. The maximum tolerated dose was 60 mg/kg. At higher dose levels, grade 3 and 4 neurological toxicity was observed, but no grade 3 or 4 hematological toxicity. The induction of hyperacetylation in peripheral blood cells was observed in the majority of patients (17).

Valproic acid in hematological cancers

Combination therapy with valproic acid has been most widely studied in hematological cancers. A total of 54 patients with relapsed or refractory leukemia were recruited to a study investigating the activity of valproic acid in combination with decitabine. The majority of patients were diagnosed with AML. In the phase I part of the study, three doses of valproic acid (20, 35 and 50 mg/kg) were studied. Treatment was administered daily for 10 days in combination with decitabine 15 mg/m^2. The phase II part of the study had a target response rate of 30%. No nonhematological dose-limiting toxicities were observed during phase I, and valproic acid was therefore administered at a dose of 50 mg/kg during phase II. Ten of 40 patients (25%) achieved a response during phase II, and the median overall survival for the whole group was 5.3 months. Histone H3 or H4 acetylation was observed in 12 of 35 (34%) patients who received valproic acid at a dose of 50 mg/kg (18, 19).

Valproic acid has also been studied in combination with ATRA in AML and myelodysplastic syndromes (MDS). A pilot study of the combination was performed in 11 elderly patients with AML who were unsuitable for intensive chemotherapy. Valproic acid was administered orally at the dose required to achieve therapeutic serum concentrations (50-100 μg/ml) for the treatment of epilepsy. ATRA 45 mg/m^2/day was administered starting 1 week after initiation of valproic acid. All patients received at least 1 month of combination therapy (median duration of therapy = 3 months). Complete marrow response was observed in 3 patients, including 1 complete remission. Two further patients had hematological improvement (20).

In another study, 23 patients with MDS and AML secondary to MDS were treated with valproic acid alone or in combination with ATRA. Valproic acid was administered orally at the dose required to achieve therapeutic serum concentrations for the treatment of epilepsy. The median treatment duration was 6 months. ATRA 80 mg/m^2/day was administered on days 1-7 of alternating weeks. Five patients were treated with the combination from the start, while other patients were treated with the combination if they did not respond or they relapsed. All patients completed at least 2 months of treatment. A response was observed in 8 (44%) patients who received valproic acid monotherapy, including 1 partial remission. Four of 5 patients who relapsed were treated with the combination, and 2 of these patients responded again. However, none of the 5 patients treated with the combination from the start showed a response. The treatments were well tolerated (21).

At the same center in Germany, the previous study was extended to 75 patients, including patients with relapsed or refractory AML. Sixty-six patients were treated with valproic acid monotherapy and 9 patients were treated with the combination from the start. Median treatment duration was 4 months for valproic acid and 2 months for ATRA. According to the International Working Group (IWG) criteria for MDS, hematological improvement was observed in 18 (24%) patients. Ten patients who responded to valproic acid subsequently relapsed, and 4 of these achieved a second response after addition of ATRA. However, patients who received the combination from the start had no additional benefit in terms of response. Response rates were strongly dependent on the disease type according to the WHO classification. There was a response rate of 52% in MDS patients with a normal blast count compared to only 16% in AML. The authors concluded that monotherapy with valproic acid was of clinical benefit in patients with low-risk MDS (22).

A similar protocol was used in 58 patients with AML who were either too old and/or medically unfit to receive intensive chemotherapy. Thirty-one patients received valproic acid as monotherapy, with ATRA added later in 13 patients who did not respond or who relapsed. Twenty-seven patients received valproic acid plus ATRA from the start. Patients received ATRA either on days 1-7 of alternating weeks (80 mg/m^2) or at a dose of 15 mg/m^2 given daily from day 4. According to the IWG criteria for AML, the response rate was only 5%, which included 1 patient with a complete remission that lasted for 16 months, 1 complete remission with incomplete recovery of blood counts and 1 partial remission. Although the authors concluded that valproic acid was not sufficiently active as single-agent therapy for AML, its use in combination with chemotherapy or demethylating agents was proposed in elderly patients unable to tolerate standard treatment regimens (23).

A study in 26 patients with poor-risk AML also found marginal antileukemic efficacy for valproic acid, with the exception of AML evolving from a myeloproliferative disorder. Patients who were unfit for or refused aggressive chemotherapy were treated with valproic acid and ATRA 45 mg/m^2/day. Nineteen patients completed at least 4 weeks' treatment and were evaluated for response. Of these, 1 patient achieved a partial remission and another had a minor response. Neurological and cardiovascular toxicity, as well as valproic acid-induced coagulopathy, were observed in a minority of patients (24).

Twenty patients aged over 60 years with recurrent or refractory AML or MDS were treated with sequential valproic acid and ATRA therapy in a phase II study. Once patients had achieved the target serum concentration of valproic acid (45-100 μg/ml), ATRA 45 mg/m^2 was added to the treatment regimen. Eleven patients were treated continuously for at least 2 months and were considered evaluable. Hematological improvement was observed in 6 patients, all of whom were evaluable. Five of these patients exhibited a major platelet response with platelet transfusion independence for at least 2 months. Three of them also exhibited a minor erythroid response. In all patients, the addition of ATRA to the treatment regimen did not modify the response observed with valproic acid alone. The most common adverse event associated with valproic acid therapy was neurological toxicity, with 4 patients experiencing grade 3 neurocortical toxicity that required withdrawal from therapy. The authors noted that

the durable platelet transfusion independence observed in some patients could reduce the burden of palliative care and improve the quality of life in elderly patients with a poor prognosis (25).

A number of studies are under way to further evaluate valproic acid in combination with other agents in hematological cancers. These include an open-label study of valproic acid with ATRA and theophyllamine in up to 30 patients with AML (26), and a phase I dose-finding study of decitabine and valproic acid in up to 84 patients with relapsed or refractory AML or previously treated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) (27). Decitabine with or without valproic acid is also being evaluated in a dose-finding study in 18-42 patients with relapsed or refractory non-Hodgkin's lymphoma (NHL) (28). An open-label study in up to 70 patients with high-risk MDS or AML treated with the combination of valproic acid, 5-azacytidine and ATRA is also ongoing (29). Two larger studies are under way in Germany and Austria. A randomized, open-label phase II study of valproic acid and ATRA and their combination in induction and consolidation therapy, as well as pegfilgrastim after consolidation therapy in younger patients with newly diagnosed AML aims to recruit 608 patients (30). A randomized, open-label phase III study in up to 500 patients is evaluating valproic acid in combination with ATRA, standard induction and consolidation therapy in older patients with newly diagnosed AML (31).

Valproic acid in solid tumors

Valproic acid has been investigated in combination with the topoisomerase II inhibitor epirubicin. A phase I/II dose-escalation study was conducted in 31 patients with metastatic solid tumors, including 9 with melanoma and 7 with breast cancer. Patients were treated with oral valproic acid at dose levels of 15, 30, 45, 60 and 75 mg/kg b.i.d. for 3 days following an i.v. loading dose, and 75 and 100 mg/kg following an oral loading dose. Epirubicin 75 or 100 mg/m^2 was infused on day 3. Treatment cycles were repeated at 3-week intervals. Recruitment is continuing up to 65 patients, and the maximum tolerated dose will also be determined as part of a multidrug regimen with 5-fluorouracil (5-FU) and cyclophosphamide. Major responses were observed in all tumor types including anthracycline failures and in anthracycline-resistant cancers. In 28 patients evaluable for response, a complete or partial response occurred in 4 (14%) patients and minor responses in 3 (11%) patients. A median of 4 treatment cycles were administered, with a median duration of response of 14 weeks (range = 12-33+). Valproic acid was associated with dose-dependent somnolence, ataxia and confusion, but it did not exacerbate epirubicin-related myelosuppression (32, 33).

A phase I study is evaluating the safety and tolerability and determining the recommended phase II dose of the combination of decitabine and valproic acid in patients with non-small cell lung cancer (NSCLC). The projected recruitment is 25 patients (34). In addition, a phase I dose-finding study is evaluating the tolerability of valproic acid in the treatment of young patients with recurrent or refractory solid tumors or CNS tumors (35).

Valproic acid in other malignancies

A phase II study is under way in treatment-naïve patients with glioblastoma multiforme who will receive valproic acid in combination with temozolomide and radiotherapy (36). The safety and efficacy of valproic acid in the induction of Epstein-Barr virus lytic cycle antigen expression in tumor tissue are also being evaluated in a phase I study in patients receiving primary therapy for

Table I: Combination therapies with valproic acid currently being investigated in clinical studies for several types of cancer (from Prous Science Integrity®).

Combination			Cancer type	Development status
Valproic acid (HDAC inhibitor)	*+ ATRA* (differentiation therapy)	*+ Standard induction/consolidation therapy*	AML, MDS	III
		or *+ 5-Azacytidine* (DNA methyltransferase inhibitor)		I/II
		or *+ theophyllamine*		I/II
	+ Decitabine (DNA methyltransferase inhibitor)		AML, CLL, SLL, NHL, NSCLC	I/II
	+ Temozolomide (DNA alkylator)		Glioblastoma multiforme	II
	+ Epirubicin (DNA topoisomerase II inhibitor)		Solid tumors	I

HDAC: histone deacetylase; ATRA: *all-trans*-retinoic acid; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; NHL: non-Hodgkin's lymphoma; NSCLC: non-small cell lung cancer.

nasopharyngeal carcinoma (37). In addition, a pilot study is evaluating valproic acid in the treatment of HIV-related Kaposi's sarcoma (38).

Ongoing clinical trials of combination therapies with valproic acid are summarized in Table I. Continuously updated information on all these clinical trials is available in Prous Science Integrity®.

Conclusions

Following promising evidence from preclinical studies in both hematological and solid tumor models, these have become active areas of research in early clinical studies with valproic acid. Completed studies, particularly in AML and MDS, have demonstrated its efficacy as monotherapy in patients with low-risk MDS. Studies in patients with high-risk MDS or AML have indicated that valproic acid in combination with ATRA or chemotherapy may be of benefit. A number of studies are being conducted to further determine the groups of patients who may benefit from combination therapy with valproic acid. In addition, early studies with epirubicin in patients with solid tumors have demonstrated promising efficacy in a number of tumor types.

Online links

An animation on " Modulation of transcriptional activation and nucleosome remodeling by histone acetylation and DNA methylation " is available for Drugs of the Future online subscribers at http://journals.prous.com

References

1. Gottlicher, M., Minucci, S., Zhu, P. et al. *Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells*. EMBO J 2001, 20(24): 6969-78.

2. Gottlicher, M. *Valproic acid: An old drug newly discovered as inhibitor of histone deacetylases.* Ann Hematol 2004, 83(Suppl. 1): S91-2.

3. Gurvich, N., Tsygankova, O.M., Meinkoth, J.L., Klein, P.S. *Histone deacetylase is a target of valproic acid-mediated cellular differentiation.* Cancer Res 2004, 64(3): 1079-86.

4. Sorbera, L.A. *Epigenetic targets as an approach to cancer therapy and prevention.* Drugs Fut 2006, 31(4): 335-44.

5. Galm, O., Herman, J.G., Baylin, S.B. *The fundamental role of epigenetics in hematopoietic malignancies.* Blood Rev 2006, 20(1): 1-13.

6. Mongan, N.P., Gudas, L.J. *Valproic acid, in combination with all-trans retinoic acid and 5-aza-2'-deoxycytidine, restores expression of silenced RARbeta2 in breast cancer cells.* Mol Cancer Ther 2005, 4(3): 477-86.

7. Takai, N., Desmond, J.C., Kumagai, T. et al. *Histone deacetylase inhibitors have a profound antigrowth activity in endometrial cancer cells.* Clin Cancer Res 2004, 10(3): 1141-9.

8. Graziani, G., Tentori, L., Portarena, I., Vergati, M., Navarra, P. *Valproic acid increases the stimulatory effect of estrogens on proliferation of human endometrial adenocarcinoma cells*. Endocrinology 2003, 144(7): 2822-8.

9. Bug, G., Gul, H., Schwarz, K. et al. *Valproic acid stimulates proliferation and self-renewal of hematopoietic stem cells.* Cancer Res 2005, 65(7): 2537-41.

10. Qi, H., Ratnam, M. *Synergistic induction of folate receptor beta by all-trans retinoic acid and histone deacetylase inhibitors in acute myelogenous leukemia cells: Mechanism and utility in enhancing selective growth inhibition by antifolates*. Cancer Res 2006, 66(11): 5875-82.

11. Knuepfer, M.M., Hernaiz-Driever, P., Poppenborg, H., Wolff, J.E., Cinatl, J. *Valproic acid inhibits proliferation and changes expression of CD44 and CD56 of malignant glioma cells in vitro*. Anticancer Res 1998, 18(5A): 3585-90.

12. Catalano, M.G., Fortunati, N., Pugliese, M., Costantino, L., Poli, R., Bosco, O., Boccuzzi, G. *Valproic acid induces apoptosis and cell cycle arrest in poorly differentiated thyroid cancer cells.* J Clin Endocrinol Metab 2005, 90(3): 1383-9.

13. Fortunati, N., Catalano, M.G., Arena, K., Brignardello, E., Piovesan, A., Boccuzzi, G. *Valproic acid induces the expression of the Na+/I- symporter and iodine uptake in poorly differentiated thyroid cancer cells*. J Clin Endocrinol Metab 2004, 89(2): 1006-9.

14. Xia, Q., Sung, J., Chowdhury, W. et al. *Chronic administration of valproic acid inhibits prostate cancer cell growth in vitro and in vivo*. Cancer Res 2006, 66(14): 7237-44.

15. Chavez-Blanco, A., Perez-Plasencia, C., Perez-Cardenas, E. et al. *Antineoplastic effects of the DNA methylation inhibitor hydralazine and the histone deacetylase inhibitor valproic acid in cancer cell lines.* Cancer Cell Int 2006, 6: 2.

16. Chavez-Blanco, A., Segura-Pacheco, B., Perez-Cardenas, E. et al. *Histone acetylation and histone deacetylase activity of magnesium valproate in tumor and peripheral blood of patients with cervical cancer. A phase I study*. Mol Cancer 2005, 4(1): 22.

17. Atmaca, A., Maurer, A., Heinzel, T. et al. *A dose-escalating phase I study with valproic acid (VPA) in patients (pts) with advanced cancer*. J Clin Oncol 2004, 22(14, Suppl.): Abst 3169.

18. Garcia-Manero, G., Kantarjian, H., Sanchez-Gonzalez, B. et al. *Results of a phase I/II study of the combination of 5-aza-2'-deoxycytidine and valproic acid in patients with acute myeloid leukemia and myelodysplastic syndrome*. 41st Annu Meet Am Soc Clin Oncol (ASCO) (May 13-17, Orlando) 2005, Abst 6544.

19. Garcia-Manero, G., Kantarjian, H., Sanchez-Gonzalez, B. et al. *Final results of a phase I/II study of the combination of the hypomethylating agent 5-aza-2'-deoxycytidine (DAC) and the histone deacetylase inhibitor valproic acid (VPA) in patients with leukaemia*. Blood [47th Annu Meet Am Soc Hematol (Dec 10-13, Atlanta) 2005] 2005, 106(11): Abst 408.

20. Raffoux, E., Chaibi, P., Dombret, H., Degos, L. *Valproic acid and all-trans retinoic acid for the treatment of elderly patients with acute myeloid leukaemia*. Haematologica 2005, 90(7): 986-8.

21. Kuendgen, A., Strupp, C., Aivado, M. et al. *Treatment of myelodysplastic syndromes with valproic acid alone or in combination with all-trans retinoic acid.* Blood 2004, 104(5): 1266-9.

22. Kuendgen, A., Knipp, S., Fox, F. et al. *Results of a phase 2 study of valproic acid alone or in combination with all-trans*

retinoic acid in 75 patients with myelodysplastic syndrome and relapsed or refractory acute myeloid leukaemia. Ann Hematol 2005, 84(Suppl. 13): 61-6.

23. Kuendgen, A. et al. *The histone deacetylase (HDAC) inhibitor valproic acid as monotherapy or in combination with all-trans retinoic acid in patients with acute myeloid leukaemia.* Cancer 2006, 106(1): 112-9.

24. Bug, G., Ritter, M., Wassmann, B. et al. *Clinical trial of valproic acid and all-trans retinoic acid in patients with poor-risk acute myeloid leukaemia.* Cancer 2005, 104(12): 2717-25.

25. Pilatrino, C., Cilloni, D., Messa, E. et al. *Increase in platelet count in older, poor-risk patients with acute myeloid leukemia or myelodysplastic syndrome treated with valproic acid and all-trans retinoic acid.* Cancer 2005, 104(1): 101-9.

26. Differentiation induction in acute myelogenous leukemia (NCT00175812). ClinicalTrials.gov Web site 2006.

27. Decitabine and valproic acid in treating patients with refractory or relapsed acute myeloid leukemia or previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma (NCT00079378). ClinicalTrials.gov Web site 2006.

28. Decitabine with or without valproic acid in treating patients with relapsed or refractory non-Hodgkin's lymphoma (NCT00109824). ClinicalTrials.gov Web site 2006.

29. Phase I/II 5-azacytidine plus VPA plus ATRA (NCT00326170). ClinicalTrials.gov Web site 2006.

30. Study on valproic acid, all-trans retinoic acid and their combination in induction and consolidation therapy as well as pegfilgrastim after consolidation therapy in younger patients with newly diagnosed acute myeloid leukemia (NCT00151242). ClinicalTrials.gov Web site 2006.

31. Study on valproic acid in combination with all-trans retinoic acid, standard induction- and consolidation therapy in older patients with newly diagnosed acute myeloid leukemia (NCT00151255). ClinicalTrials.gov Web site 2006.

32. Munster, P.N., Marchion, D.C., Bicaku, E. et al. *Pharmacokinetic and pharmacodynamic analysis of the histone deacetylase inhibitor, valproic acid in combination with the topoisomerase II inhibitor, epirubicin in solid tumor malignancies.* 17th AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 14-18, Philadelphia) 2005, Abst B164.

33. Phase I trial of valproic acid and epirubicin in solid tumor malignancies (NCT00246103). ClinicalTrials.gov Web site 2006.

34. Decitabine and valproic acid in treating patients with non-small cell lung cancer (NCT00084981). ClinicalTrials.gov Web site 2006.

35. Valproic acid in treating young patients with recurrent or refractory solid tumors or CNS tumors (NCT00107458). ClinicalTrials.gov Web site 2006.

36. Valproic acid, temozolomide, and radiation therapy in treating patients with glioblastoma multiforme (NCT00313664). ClinicalTrials.gov Web site 2006.

37. Valproic acid in the induction of EBV lytic cycle antigen expression in nasopharyngeal carcinoma (NCT00181220). ClinicalTrials.gov Web site 2006.

38. *Valproic acid in treating patients with Kaposi's sarcoma (NCT00075777).* ClinicalTrials.gov Web site 2006.