

## Review Articles

# Extramedullary Disease in Acute Promyelocytic Leukemia: Two-In-One Disease

Francesco Albano and Giordina Specchia

Ematologia con Trapianto, Università degli Studi di Bari "Aldo Moro"

Correspondence to: G. Specchia, Ematologia con Trapianto, Università degli Studi di Bari "Aldo Moro". E-mail: [g.specchia@ematba.uniba.it](mailto:g.specchia@ematba.uniba.it)

**Competing interests:** The authors have declared that no competing interests exist.

Published: December 21, 2011

Received: October 30, 2011

Accepted: November 27, 2011

Mediterr J Hematol Infect Dis 2011, 3(1): e2011066, DOI 10.4084/MJHID.2011.066

This article is available from: <http://www.mjhid.org/article/view/9480>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Abstract.** In acute promyelocytic leukemia (APL), extramedullary disease (EMD) is particularly rare and shows special clinical and biological features. It is estimated that about 3–5% of APL patients will suffer extramedullary relapse. The most common site of EMD in APL is the central nervous system (CNS). At present, there are still many issues of EMD in APL needing further clarification, including pathogenesis, risk factors, prognosis and treatment. A better understanding of the biological mechanisms underlying EMD is important to be able to devise more effective CNS prophylaxis and induction-consolidation therapeutic strategies.

**Introduction.** Acute leukemia may present in a variety of extramedullary tissues with or without bone marrow disease. Extramedullary involvement by acute leukemia is a relatively rare but clinically significant phenomenon that often poses diagnostic and therapeutic dilemmas. Myeloid sarcoma and leukemia cutis are two well-known EM manifestations. Extramedullary disease (EMD) in acute promyelocytic leukemia (APL) is particularly rare and shows special clinical and biological features.

**How common is EMD in APL?** The combination of all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy, together with maintenance treatment, has improved the outcome of APL. In fact, approximately 90% of patients with newly diagnosed APL achieve complete remission (CR).<sup>1,2</sup> and it is estimated that 70–80% of these patients will remain in remission.<sup>1,3</sup> However, approximately 20–30% of

patients will eventually relapse.<sup>2</sup> EMD is a rare complication in APL: it is estimated that about 3–5% of patients will suffer extramedullary relapse.<sup>4-6</sup> However, since the introduction of ATRA in the treatment of patients with APL, EMD disease has been increasingly reported; in fact, in the literature fewer than 25 well-documented cases had been described before 1995.<sup>7</sup> This is most likely in part due to the following reasons:

- APL patients may develop EMD more frequently because they are achieving longer survival times thanks to improved treatment regimens.
- It is possible that the drugs employed in the induction regimens (ATRA, anthracycline and arsenic trioxide) do not reach therapeutic concentrations at the anatomical sites where EMD eventually develops.
- It is also possible that ATRA therapy might contribute to extramedullary relapses by

modulating and upregulating the expression of adhesion molecules on leukemic cells.

EMD commonly occurs within 1 year of achieving CR, but it can appear at any time during the disease course and can be isolated or can precede systemic relapse.<sup>2,6</sup> As to cases of EMD at APL presentation, although a few anecdotal reports have been made this observation is very uncommon.<sup>8</sup>

#### **What are the most frequent anatomical sites of EMD in APL?**

The most frequent site of EMD in APL patients is the central nervous system (CNS) and at least 10% of hematologic relapses are accompanied by CNS involvement.<sup>9</sup> CNS relapse appears in around 1% of APL patients and may occur despite hematological remission.<sup>6,10-12</sup> The skin is the second most common site of EMD.<sup>2</sup> The increased frequency of EMD especially in these two sites could be explained by some biological effects of ATRA induction treatment. In fact, ATRA-driven differentiation of APL cells is associated with a significant upregulation of cellular adhesion molecules expressed on the cell surface, like LFA-1 and VLA-4.<sup>13</sup> The mechanism of APL blasts adhesion to the endothelium may be further increased by interleukin-1, via an effect which may be mediated through an increased expression of ICAM-1 and VCAM-1 on the endothelial cell surface.<sup>14</sup> These surface proteins have both been demonstrated on the CNS endothelium and have been implicated in the migration processes of leukocytes across the blood-brain barrier (BBB), through interactions with LFA-1 and VLA-4, respectively.<sup>9</sup> Since both LFA-1 and VLA-4 are upregulated in APL blasts treated with retinoids, it is reasonable to suppose that the upregulation of these adhesion molecules may promote passage across the BBB of ATRA-treated APL cells, thereby creating the conditions for a subsequent CNS relapse (**Figure 1**). Moreover, ATRA also stimulates keratinocytes to proliferate and upregulate their expression of ICAMs.<sup>9</sup> It has been suggested that the migration of leukemic cells into the skin and other tissues during ATRA induction treatment may leave a reservoir of viable leukemic cells in these sites, that eventually may proliferate and cause EMD. These biological events could account for the clinical observation of a preferential skin localization of APL cells relapsing after ATRA treatment. Moreover, a high frequency of EMD in APL may also be related to the ATRA-induced upregulation of G-CSF receptors in APL cells, making them more sensitive to endogenous or exogenous G-CSF effects.<sup>15</sup> Other described sites of EMD in APL include: the testes, sites of vascular access, external ear and auditory canal, lung, pleura, heart, lymph nodes, mediastinum, thymus, spine, breast, pelvis, mandible and gingiva, bowel. Since in

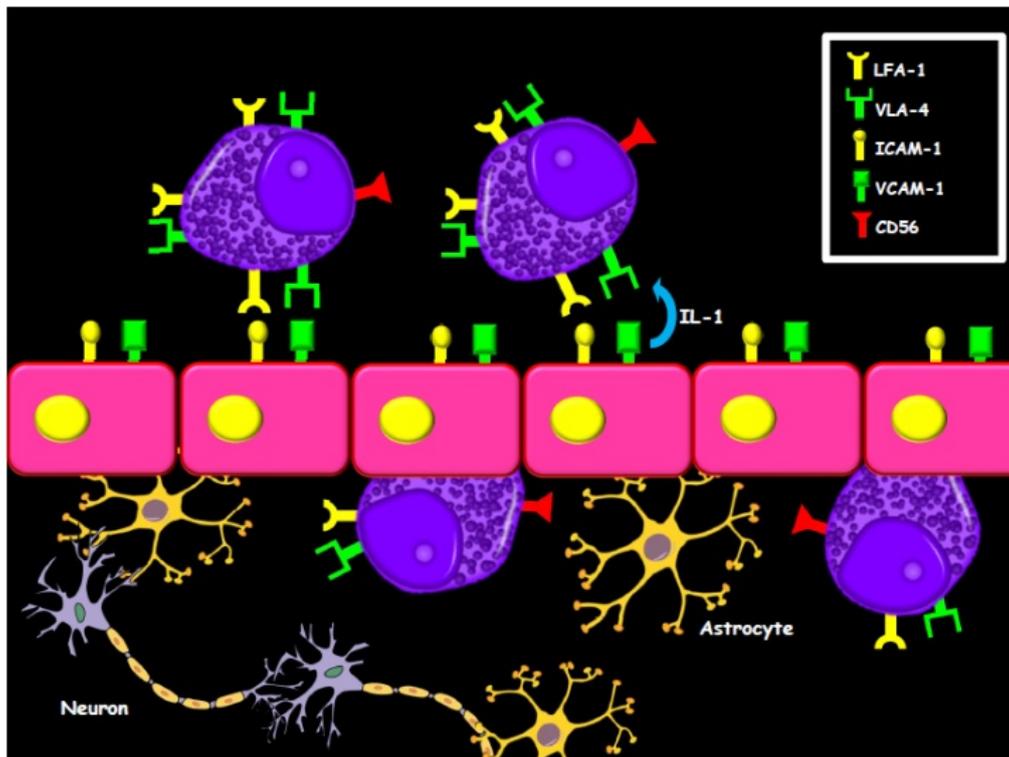
patients affected by ATRA syndrome APL cells infiltrate multiple tissues and organs, it has been hypothesized that ATRA could promote the migration of differentiating blasts into several tissues, constituting a reservoir of viable leukemic cells. These cells could later proliferate and result in an extramedullary recurrence.<sup>16-17</sup> However, the issue as to whether ATRA promotes EMD in APL is still highly controversial, since several studies have reached different conclusions.<sup>5-7,18-19</sup>

#### **Are there risk factors for an EMD onset in APL?**

Several factors have been associated with a higher risk of extramedullary relapse such as younger age (<45 years), a high WBC count at diagnosis, microgranular morphology, expression of CD2 and/or CD56, PML-RAR $\alpha$  bcr3 isoform expression, ATRA syndrome, monotherapy regimens, and the use of therapy schedules that exclude cytarabine.<sup>2,4,12,20-21</sup> Moreover, two recent studies<sup>4,22</sup> reported a significantly higher incidence of CNS involvement in patients with an initial WBC of more than  $10 \times 10^9/L$ . In addition to hyperleukocytosis, the PETHEMA study also identified a previous CNS hemorrhage during induction as an independent risk factor for CNS relapse.<sup>22</sup> It has recently been demonstrated that CD56+ APL has a greater risk of extramedullary relapse.<sup>21</sup> The higher frequency of coexpression of stem cell (CD117) and NK-cell antigens (CD2, CD7) in CD56+ APL cells suggests that in some of these cases APL might have arisen in progenitors that did not undergo lineage restriction.<sup>23</sup> Therefore, it is possible that CD56+ APL may emerge from a more immature, undifferentiated and pluripotent leukemic stem cell that is less sensitive to the combination of ATRA and anthracyclines. This could explain the higher frequency of extramedullary relapse in these cases.<sup>21,24-25</sup>

#### **What is the prognosis of EMD in APL? Which is the best therapy?**

Because of the rarity of the disease, the prognosis of patients with EMD in APL is still unclear. The GIMEMA study<sup>6</sup> reported that the outcome was similar to that of patients who experienced isolated bone marrow relapse, whereas in the joint study by the PETHEMA and the European APL groups<sup>4</sup> it was found that patients with an extramedullary relapse had a poorer outcome. EMD can occur in isolation or associated with bone marrow involvement as a first relapse, but also after one or more hematologic relapses. The molecular status in the peripheral blood/bone marrow did not seem to predict the possibility of EMD relapse.<sup>5-6</sup> Management of relapse in the CNS and other extramedullary sites in APL patients is a challenging issue on which there is a strong need for further data. The optimal management



**Figure 1.** ATRA-driven differentiation of APL cells is associated with the upregulation of cellular adhesion molecules like LFA-1 and VLA-4. The mechanism of APL blasts adhesion to the endothelium may be further increased by interleukin-1, an effect which may be mediated via an increased expression of ICAM-1 and VCAM-1 on the CNS endothelium. Since both LFA-1 and VLA-4 are upregulated in APL blasts treated with retinoids, it is reasonable to suppose that the upregulation of these adhesion molecules might promote passage across the BBB of ATRA-treated APL cells, thereby creating the conditions for a subsequent CNS relapse. Moreover, CD56 expression on APL cells may also foster CNS relapse.

of APL patients in different situations has not been critically assessed.<sup>26</sup> Because the majority of CNS relapses occurs in APL patients with hyperleukocytosis,<sup>4</sup> CNS prophylaxis for patients in this particular high-risk setting may be appropriate.<sup>26</sup> In these cases CNS prophylaxis should be performed after the achievement of CR because lumbar puncture at presentation and during induction is extremely hazardous. However, the benefit of this kind of strategy has not yet been clearly established.

The role of ATRA and arsenic trioxide in the therapeutic management of CNS relapse is still unclear because it is not known whether these drugs cross the BBB; nevertheless, some authors have reported responses to these agents in patients with meningeal disease.<sup>27-28</sup> This may be due to the EMD disrupting the BBB. Arsenic trioxide has also been reported to cross the BBB and may be useful as a therapeutic agent to control CNS relapse.<sup>29</sup> On the other hand, some reports have confirmed that although arsenic crosses the BBB when administered intravenously, the concentration in CSF is probably not sufficient to treat meningeal leukemia.<sup>30-31</sup> Recently, as induction treatment of CNS relapse, the European LeukemiaNet recommendations<sup>26</sup> proposed a schedule of weekly triple intrathecal therapy (ITT) with methotrexate, hydrocortisone, and cytarabine until complete

clearance of blasts in the cerebrospinal fluid (CSF), followed by 6 to 10 more spaced-out ITT treatments as consolidation. In these cases systemic treatment should also be given because CNS disease is almost invariably associated with hematologic or molecular relapse in the marrow. Chemotherapy regimens with high CNS penetrance, such as high-dose cytarabine, have been used in this situation. In patients responding to treatment, allogeneic or autologous transplant is then recommended as consolidation treatment, together with craniospinal irradiation. It was demonstrated that cytarabine during consolidation treatment significantly reduced the relapse rate in high-risk APL patients.<sup>32-33</sup> Because of the limited numbers of EMD events reported in these studies, it is very hard to draw firm conclusions regarding the best schedule of cytarabine to use in the consolidation regimen to prevent the EMD in APL. In cases of promyelocytic sarcoma, wherever it is localized, radiation and intensive systemic therapy might be considered. Recently, successful treatment of relapsed and refractory EMD with Tamibarotene,<sup>34</sup> a synthetic retinoid approved in Japan for use in relapsed/refractory APL, has been reported.<sup>35</sup> Tamibarotene is 10 times more potent than ATRA as an inducer of HL-60 and NB-4 leukemia cell lines differentiation. While tamibarotene has displayed a significant activity in bone marrow-relapsed APL, its

efficacy in EMD needs to be confirmed in further studies.

**Conclusions.** At present, there are still many open issues on EMD in APL patients. However, some

aspects are becoming clearer. An improved understanding of the biological mechanisms that underlie EMD should allow us to devise more effective prophylaxis and induction therapeutic strategies against this severe clinical presentation.

## References:

1. Wang ZY, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. *Blood*. 2008;111:2505–15 <http://dx.doi.org/10.1182/blood-2007-07-102798> PMID:18299451
2. Tallman MS. Treatment of relapsed or refractory acute promyelocytic leukemia. *Best Pract Res Clin Haematol*. 2007;20:57–65 <http://dx.doi.org/10.1016/j.beha.2006.11.002>
3. Lengfelder E, Saussele S, Weisser A, Buchner T, Hehlmann R. Treatment concepts of acute promyelocytic leukemia. *Crit Rev Oncol Hematol*. 2005;56:261–74 <http://dx.doi.org/10.1016/j.critrevonc.2004.08.009> PMID:16236522
4. de Botton S, Sanz MA, Chevret S, Dombret H, Martin G, Thomas X, Mediavilla JD, Recher C, Ades L, Quesnel B, Brault P, Fey M, Wandt H, Machover D, Guerci A, Maloisel F, Stoppa AM, Rayon C, Ribera JM, Chomienne C, Degos L, Fenaux P; European APL Group; PETHEMA Group. Extramedullary relapse in acute promyelocytic leukemia treated with all-trans retinoic acid and chemotherapy. *Leukemia*. 2006;20:35–41 <http://dx.doi.org/10.1038/sj.leu.2404006> PMID:16307026
5. Vega-Ruiz A, Faderl S, Estrov Z, Pierce S, Cortes J, Kantarjian H, Ravandi F. Incidence of extramedullary disease in patients with acute promyelocytic leukemia: a single-institution experience. *Int J Hematol*. 2009;89:489–496 <http://dx.doi.org/10.1007/s12185-009-0291-8> PMID:19340529
6. Specchia G, Lo Coco F, Vignetti M, Avvisati G, Fazi P, Albano F, Di Raimondo F, Martino B, Ferrara F, Selleri C, Liso V, Mandelli F. Extramedullary involvement at relapse in acute Incidence of extramedullary disease in acute promyelocytic leukemia patients promyelocytic leucemia patients treated or not with all-trans retinoic acid: a report by the Gruppo Italiano Malattie Ematologiche dell'Adulto. *J Clin Oncol*. 2001;19:4023–8 PMID:11600603
7. Wiernik PH, De Bellis R, Muxi P, Dutcher JP. Extramedullary acute promyelocytic leukemia. *Cancer*. 1996 78:2510-2514 [http://dx.doi.org/10.1002/\(SICI\)1097-0142\(19961215\)78:12<2510::AID-CNCR10>3.0.CO;2-Z](http://dx.doi.org/10.1002/(SICI)1097-0142(19961215)78:12<2510::AID-CNCR10>3.0.CO;2-Z)
8. Worch J, Ritter J, Fruhwald MC. Presentation of acute promyelocytic leukemia as granulocytic sarcoma. *Pediatr Blood Cancer*. 2008;50:657–60 <http://dx.doi.org/10.1002/pbc.21190>
9. Evans GD, Grimwade DJ. Extramedullary disease in acute promyelocytic leukemia. *Leuk Lymphoma*. 1999;33:219-229 PMID:10221502
10. Liso V, Specchia G, Pogliani EM, Palumbo G, Mininni D, Rossi V, Teruzzi E, Mestice A, Coppi MR, Biondi A. Extramedullary involvement in patients with acute promyelocytic leukemia: a report of seven cases. *Cancer*. 1998; 83: 1522–1528 [http://dx.doi.org/10.1002/\(SICI\)1097-0142\(19981015\)83:8<1522::AID-CNCR6>3.0.CO;2-4](http://dx.doi.org/10.1002/(SICI)1097-0142(19981015)83:8<1522::AID-CNCR6>3.0.CO;2-4)
11. Burry LD, Seki JT. CNS relapses of acute promyelocytic leukemia after all-trans retinoic acid. *Ann Pharmacother* 2002; 36: 1900–1906 <http://dx.doi.org/10.1345/aph.1A471> PMID:12452754
12. Breccia M, Carosino I, Diverio D, De Santis S, De Propriis MS, Romano A, Petti MC, Mandelli F, Lo-Coco F. Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count. *Br J Haematol* 2003; 120: 266–270 <http://dx.doi.org/10.1046/j.1365-2141.2003.04056.x> PMID:12542484
13. Di Noto R, Lo Prado C, Schiavone EM, Ferrara F, Manzo C, Vacca C, Del Vecchio L. All-trans retinoic acid (ATRA) and the regulation of adhesion molecules in acute myeloid leukemia. *Leuk Lymphoma* 1996; 21: 201–209 <http://dx.doi.org/10.3109/10428199209067601> PMID:8726400
14. Marchetti M, Falanga A, Giovanelli S, Oldani E, Barbui T. All-trans-retinoic acid increases adhesion to endothelium of the human promyelocytic leukaemia cell line NB4. *Br J Haematol* 1996; 93: 360–366. <http://dx.doi.org/10.1046/j.1365-2141.1996.4911029.x> PMID:8639429
15. de Gentile A, Toubert ME, Dubois C, Krawice I, Schlageter MH, Balitrand N, Castaigne S, Degos L, Rain JD, Najean Y. Induction of high-affinity GM-CSF receptors during all-trans retinoic acid treatment of acute promyelocytic leukemia. *Leukemia* 1994; 8: 1758–1762 PMID:7934172
16. Raanani P, Shpillerberg O, Ben-Bassat I. Extramedullary disease and targeted therapies for hematological malignancies—is the association real? *Ann Oncol*. 2007;18:7–12 <http://dx.doi.org/10.1093/annonc/mdl129> PMID:16790518
17. Ko BS, Tang GL, Chen YC, Yao M, Wang CH, Shen MC, Tien HF. Extramedullary relapse after all-trans retinoic acid treatment in acute promyelocytic leukemia. The occurrence of retinoic acid syndrome is a risk factor. *Leukemia* 1999; 13: 1406–1408 <http://dx.doi.org/10.1038/sj.leu.2401495> PMID:10482992
18. Tsimberidou AM, Estey E, Whitman GJ, Dryden MJ, Ratnam S, Pierce S, Faderl S, Giles F, Kantarjian HM, Garcia-Manero G. Extramedullary relapse in a patient with acute promyelocytic leukemia: successful treatment with arsenic trioxide, all-trans retinoic acid and gemtuzumab ozogamicin therapies. *Leuk Res* 2004;28: 991–994 <http://dx.doi.org/10.1016/j.leukres.2004.01.004> PMID:15234578
19. Ohno R, Asou N, Ohnishi K. Treatment of acute promyelocytic leukemia: strategy toward further increase of cure rate. *Leukemia* 2003; 17: 1454–1463 <http://dx.doi.org/10.1038/sj.leu.2403031> PMID:12886231
20. Ades L, Sanz Miguel A, Chevret S, Montesinos P, Chevallier P, Raffoux E, Vellenga E, Guerci A, Pigneux A, Hugué F, Rayon C, Stoppa AM, de la Serna J, Cahn JY, Meyer-Monard S, Pabst T, Thomas X, de Botton S, Parody R, Bergua J, Lamy T, Vekhoff A, Negri S, Ifrah N, Dombret H, Ferrant A, Bron D, Degos L, Fenaux P. Treatment of newly diagnosed acute promyelocytic leukemia (APL): a comparison of French–Belgian–Swiss and Pethema results. *Blood*. 2008;111:1078–84 <http://dx.doi.org/10.1182/blood-2007-07-099978> PMID:17975017
21. Montesinos P, Rayón C, Vellenga E, Brunet S, González J, González M, Holowiecka A, Esteve J, Bergua J, González JD, Rivas C, Tormo M, Rubio V, Bueno J, Manso F, Milone G, de la Serna J, Pérez I, Pérez-Encinas M, Krsnik I, Ribera JM, Escoda L, Lowenberg B, Sanz MA; PETHEMA; HOVON Groups. Clinical significance of CD56 expression in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline-based regimens. *Blood*. 2011; 117:1799-805 <http://dx.doi.org/10.1182/blood-2010-04-277434> PMID:21148082
22. Montesinos P, Diaz-Mediavilla J, Debèn G, Prates V, Tormo M, Rubio V, Pérez I, Fernández I, Viguria M, Rayón C, González J, de la Serna J, Esteve J, Bergua JM, Rivas C, González M, González JD, Negri S, Brunet S, Lowenberg B, Sanz MA. Central nervous system involvement at first relapse in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline monochemotherapy without intrathecal prophylaxis. *Haematologica*. 2009; 94:1242-1249, <http://dx.doi.org/10.3324/haematol.2009.007872> PMID:19608685 PMID:2738716
23. Albano F, Mestice A, Pannunzio A, Lanza F, Martino B, Pastore D, Ferrara F, Carluccio P, Nobile F, Castoldi G, Liso V, Specchia G. The biological characteristics of CD34+ CD2+ adult acute promyelocytic leukemia and the CD34 CD2 hypergranular (M3) and microgranular (M3v) phenotypes. *Haematologica*. 2006; 91:311-316. PMID:16531253
24. Ferrara F, Morabito F, Martino B, Specchia G, Liso V, Nobile F, Boccuni P, Di Noto R, Pane F, Annunziata M, Schiavone EM, De Simone M, Guglielmi C, Del Vecchio L, Lo Coco F. CD56

- expression is an indicator of poor clinical outcome in patients with acute promyelocytic leukemia treated with simultaneous all-trans-retinoic acid and chemotherapy. *J Clin Oncol.* 2000;18:1295-1300 PMID:10715300
25. Ito S, Ishida Y, Oyake T, Satoh M, Aoki Y, Kowata S, Uchiyama T, Enomoto S, Sugawara T, Numaoka H, Suzuki K, Murai K. Clinical and biological significance of CD56 antigen expression in acute promyelocytic leukemia. *Leuk Lymphoma.* 2004; 45:1783-1789. <http://dx.doi.org/10.1080/10428190410001683624>
  26. Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, Naoe T, Lengfelder E, Büchner T, Döhner H, Burnett AK, Lo Coco F. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. *Blood.* 2009; 26:113:1875-91. <http://dx.doi.org/10.1182/blood-2008-04-150250> PMID:18812465
  27. Patriarca F, Fili C, Antonella G, Sperotto A, Prosdocimo S, Fanin R. Activity of all-trans-retinoic acid in a case of central nervous system extramedullary relapse of acute promyelocytic leukemia. *Eur J Haematol.* 2002; 68:310-3 <http://dx.doi.org/10.1034/j.1600-0609.2002.01660.x> PMID:12144538
  28. Burry LD, Seki JT. CNS relapses of acute promyelocytic leukemia after all-trans retinoic acid. *Ann Pharmacother.* 2002;36:1900-6 <http://dx.doi.org/10.1345/aph.1A471> PMID:12452754
  29. Kiguchi T, Yoshino Y, Yuan B, Yoshizawa S, Kitahara T, Akahane D, Gotoh M, Kaise T, Toyoda H, Ohyashiki K. Speciation of arsenic trioxide penetrates into cerebrospinal fluid in patients with acute promyelocytic leukemia. *Leuk Res.* 2010; 34:403-5 <http://dx.doi.org/10.1016/j.leukres.2009.08.001> PMID:19733394
  30. Knipp S, Gatterman N, Schapira M, Käferstein H, Germing U. Arsenic in the cerebrospinal fluid of a patient receiving arsenic trioxide for relapsed acute promyelocytic leukemia with CNS involvement. *Leuk Res.* 2007;31:1585-7 <http://dx.doi.org/10.1016/j.leukres.2007.03.007> PMID:17416415
  31. Helwig A, Klemm M, Schuttig R, Röllig C, Wassilew N, Ehninger G, Illmer T. Arsenic-induced APL differentiation in cerebrospinal fluid. *Leuk Res.* 2007; 31:703-5 <http://dx.doi.org/10.1016/j.leukres.2006.06.011> PMID:16876245
  32. Lo-Coco F, Avvisati G, Vignetti M, Breccia M, Gallo E, Rambaldi A, Paoloni F, Fioritoni G, Ferrara F, Specchia G, Cimino G, Diverio D, Borlenghi E, Martinelli G, Di Raimondo F, Di Bona E, Fazi P, Peta A, Bosi A, Carella AM, Fabbiano F, Pogliani EM, Petti MC, Amadori S, Mandelli F; Italian GIMEMA Cooperative Group. Front-line treatment of acute promyelocytic leukemia with AIDA induction followed by risk-adapted consolidation for adults younger than 61 years: results of the AIDA-2000 trial of the GIMEMA Group. *Blood* 2010; 116:3171-9 <http://dx.doi.org/10.1182/blood-2010-03-276196> PMID:20644121
  33. Sanz MA, Montesinos P, Rayón C, Holowiecka A, de la Serna J, Milone G, de Lisa E, Brunet S, Rubio V, Ribera JM, Rivas C, Krsnik I, Bergua J, González J, Díaz-Mediavilla J, Rojas R, Manso F, Ossenkoppele G, González JD, Lowenberg B; PETHEMA and HOVON Groups. Risk-adapted treatment of acute promyelocytic leukemia based on all-trans retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. *Blood.* 2010;115:5137-46 <http://dx.doi.org/10.1182/blood-2010-01-266007> PMID:20393132
  34. Naina HV, Levitt D, Vusirikala M, Anderson LD Jr, Scaglioni PP, Kirk A, Collins RH Jr. Successful treatment of relapsed and refractory extramedullary acute promyelocytic leukemia with tamibarotene. *J Clin Oncol.* 2011; 29:e534-6 <http://dx.doi.org/10.1200/JCO.2011.34.8953> PMID:21482998
  35. Tobita T, Takeshita A, Kitamura K, Ohnishi K, Yanagi M, Hiraoka A, Karasuno T, Takeuchi M, Miyawaki S, Ueda R, Naoe T, Ohno R. Treatment with a new synthetic retinoid, Am80, of acute promyelocytic leukemia relapsed from complete remission induced by all-trans retinoic acid. *Blood.* 1997; 90:967-973 PMID:9242525