**Extramedullary disease and targeted therapies for hematological malignancies—is the association real?**

**P. Raanani**, O. Shpilberg & I. Ben-Bassat

1Institute of Hematology, Rabin Medical Center, Beilinson Campus, Petah-Tikva; 2Institute of Hematology, The Chaim Sheba Medical Center, Tel-Hashomer and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Received 31 March 2006; accepted 28 April 2006

During the past years targeted therapies have gained a major role in the treatment of cancer patients, including those with hematological malignancies. Extramedullary involvement is a rare manifestation of acute and chronic leukemias and of multiple myeloma. Nevertheless, with the expanding use of targeted treatments there is an impression that the incidence of extramedullary relapses is increasing. We reviewed the reports on this phenomenon in patients treated with all-trans-retinoic acid and arsenic trioxide for acute promyelocytic leukemia, thalidomide and bortezomib for multiple myeloma and imatinib for chronic myeloid leukemia. The pathogenetic mechanisms suggested are: life prolongation by these treatments allowing for disease progression arising from dormant cells; poor penetration of the drugs to sanctuary sites like the central nervous system; the requirement of some of these drugs, especially thalidomide, for the marrow microenvironment to exert their action; and finally, a possible active role for some of the drugs, like all-trans-retinoic acid. Since the use of these targeted therapies is expanding we should be aware of this association.

**Key words:** extramedullary, targeted therapy, ATRA, thalidomide, imatinib

---

**introduction**

During the past two decades, sophisticated targeted therapies have emerged as an alternative and complementary option to conventional chemotherapy in cancer patients. The main target organ for treatment in hematological malignancies is the bone marrow. This is true especially for leukemia and multiple myeloma, disorders involving mainly and almost exclusively this area. Extramedullary relapse was a rare manifestation of these disorders. However, it is our impression that since the introduction of the novel agents to the armamentarium of hematological malignancies it is becoming more common.

We have reviewed the possible relationship between extramedullary disease (EMD) of hematological malignancies primarily involving the bone marrow and treatment with the following agents: all-trans-retinoic acid (ATRA) and arsenic trioxide (ASO) for acute promyelocytic leukemia (APL), thalidomide and bortezomib for multiple myeloma (MM) and imatinib for chronic myeloid leukemia (CML).

We suggest a common denominator for the tendency of some of these agents to be associated with EMD despite a good response in the bone marrow.

---

**extramedullary disease in various targeted therapies**

**All-Trans-Retinoic Acid (ATRA)**

The largest number of reports regarding EMD associated with targeted therapies has been with ATRA. The reason might be that ATRA was the first agent of this group of drugs to be used in hematological malignancies.

EMD has been reported to occur in 3%–8% of patients with APL. Around 70 cases have been reported in the literature so far and have been reviewed previously in several publications [1–28]. EM infiltration in APL may occur at presentation, during treatment or in relapse. It may be an isolated event or it may precede systemic relapse [25]. A common feature of EM recurrences is a short progression-free time after the first remission, usually less than 1 year [8, 17, 24], with some cases developing during consolidation treatment [4, 24]. The EM sites reported are central nervous system (CNS), skin, middle and external ear, lung, pleura, lymph node, mediastinum, thymus, spine, breast, pelvis, mandible and gingiva, with the CNS and skin being the most common sites [5, 13, 26]. CNS relapse occurs in around 1% of patients with APL and it may occur despite hematological remission [13, 22, 26, 29].

The occurrence of EMD has long been considered a rare event in APL patients treated with chemotherapy alone, whereas this phenomenon has increasingly been reported in the ATRA era [5, 13, 21]. The question arises as to whether treatment...
of APL with ATRA predisposes patients to the development of EMD [21, 26]. This question is still open, as various trials have shown contrasting results.

Wiernik et al. [5] suggested that extramedullary APL occurs more frequently after ATRA than other therapy. Ko et al. [16] demonstrated that patients receiving ATRA induction had a 2.1 increased relative risk of EMD compared with those with chemotherapy alone. In a literature review by Bae et al. [26], only three of 21 cases with CNS relapse received systemic chemotherapy without ATRA. Among 172 patients with APL treated at MDACC between 1980 and 2003, a total of three patients relapsed with isolated EMD and it occurred exclusively in patients who had received ATRA-containing induction regimens [27]. Ohno et al. [30] noted that EM relapse was absent from all 37 patients with relapsing APL in the Japanese chemotherapy only studies, while it was seen in 8% of 121 patients in the chemotherapy plus ATRA protocols.

Different conclusions were reached by the Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA). In a large study they analyzed the risk of developing EMD in APL patients enrolled onto two consecutive studies of GIMEMA: the LAP0389 protocol consisted of chemotherapy alone and the AIDA protocol consisted of chemotherapy plus ATRA. According to the results of this study there was no increased EMD risk in APL patients receiving ATRA compared with those treated with chemotherapy alone [21]. The overall rate of recurrence with EMD localization was similar in the two protocols: 2.7% and 2.2%, respectively. However, the proportion of CNS disease at relapse was significantly higher in the AIDA (8%) than in the LAP0389 study (1%), while the proportion of EMD in sites other than the CNS was similar in the two studies [21].

Several mechanisms could contribute to the development of EMD in APL patients treated with ATRA. Alternatively, it may be that more cases are being described as a consequence of an increased risk exposure, which in turn is due to prolonged survival of patients receiving modern ATRA-containing therapies with the emergence of leukemia from sanctuaries that otherwise did not have the opportunity to appear [21, 27, 28].

ATRA-driven differentiation of APL cells is accompanied by significant up-regulation of cellular adhesion molecules expressed on the cell surface like CD11b, CD11c, CD13, CD56, LFA-10 and VLA-4 molecules [14, 21, 22, 31]. Adherence of APL blasts to the endothelium may be further augmented by interleukin-1, an effect which may be mediated through increased expression of ICAM-1 and VCAM-1 on the endothelial cell surface [14, 32]. ICAM-1 and VCAM-1 have both been demonstrated on the CNS endothelium and have been implicated in the migration of leukocytes across the blood–brain barrier (BBB), through interactions with LFA-1 and VLA-4, respectively [14]. Since both LFA-1 and VLA-4 are up-regulated in APL blasts treated with retinoids, it is possible that a similar process may facilitate the penetration of the BBB by ATRA-treated APL cells, thereby creating a sanctuary site for subsequent CNS relapse. In addition, ATRA also stimulates keratinocytes to proliferate and up-regulate their expression of ICAMs [14, 22, 25]. It has been suggested that the migration of leukemic cells into the skin and other tissues during induction with ATRA may leave a reservoir of viable leukemic cells in these sites that eventually may proliferate and cause relapse.

These biological events may account for the clinical observation of preferential skin localization of APL cells relapsing after ATRA-induced i.e. induced remissions [14, 25]. On the other hand a high frequency of EM leukemic infiltrates in APL treated with ATRA may also be related to the up-regulation of G-CSF receptors in APL cells by ATRA, thereby rendering them more sensitive to endogenous or exogenous G-CSF [25, 33].

The occurrence of the ATRA syndrome was recognized to be a significant risk factor for EM involvement at relapse [24]. Since APL cells, in patients affected by ATRA syndrome, infiltrate multiple tissues and organs, including lung and skin, it was hypothesized that ATRA could promote the migration of differentiating blasts into skin, CNS and other tissues which represented a reservoir of viable blasts. These cells could later proliferate and result in an EM recurrence [10, 13, 14, 16, 24]. Others have found that a high WBC on presentation was a risk factor [28]. ATRA could promote EMD by further causing leukocytosis. Other mechanisms reported as risk factors for EMD in APL patients, such as tissue injury due to bone marrow aspiration or Hickman line insertion or seeding of a site by hemorrhage at presentation [2, 6, 9, 14, 19, 27], are irrelevant to the association between EMD and targeted therapy and, therefore, will not be discussed here.

Finally, Ohno et al. [30] raised the possibility that the doses of chemotherapy given with ATRA-based regimens are less intensive than those previously used and thus may not reach therapeutic levels in the EM tissues. This could be particularly relevant to protocols without cytarabine.

Even though the possibility of an increased risk of EMD after ATRA treatment remains an unresolved subject of discussion in the literature, a small number of reports claim that ATRA is a therapeutic option for EMD of APL as well [24]. Although in most cases ATRA was used with other modalities and its specific role is hard to assess. The successful treatment of patients with EM APL using ATRA, suggests a cyto-differentiating effect on leukemic cells at EM sites [2, 9, 10, 12]. A potential role for ATRA in the treatment of CNS relapse is of interest given that previous pharmacokinetic studies have suggested that ATRA does not cross the intact BBB [14, 34]. However, despite these pharmacokinetic data, ATRA has been reported to induce differentiation of APL blasts detected in the cerebrospinal fluid (CSF) of patients with CNS relapse [2, 5, 9, 10, 12, 22]. Selleri et al. [12] reported that prolonged ATRA led to complete resolution of biopsy proven leukemia cutis, while Lederman et al. [4] described differentiation of APL cells in the CSF following treatment with ATRA in combination with steroids and radiotherapy. Thomas et al. [9] reported on successful clinical outcome using ATRA followed by chemotherapy in a patient suffering cyto genetic and EMD of APL previously treated with ATRA.

arsenic trioxide (ASO)

ASO is also a novel alternative for APL. A link between EMD and prior treatment with ASO is suggested by reports on CNS
thalidomide

EM involvement by MM has been reported in 15%–20% of patients at diagnosis and in an additional 15% during the course of the disease [37, 38].

The association of thalidomide and EMD became apparent when reports on the lack of efficacy of thalidomide in patients with MM and EM involvement appeared. Julusson et al. [39] first described a patient who developed paraspinal plasmacytoma despite of a rapid major response of her IgA paraprotein level. Blade et al. [40] reported that five out of 17 patients with progressive MM had EM plasmacytomas at the time of the initiation of treatment with thalidomide. None of the five patients with EM plasmacytomas responded, compared with nine of 12 patients without evidence of EMD. In a later comment, Myers et al. [41] reported three similar cases showing a lack of response to thalidomide in the plasmacytomas but a marked improvement in the abnormal protein levels. We have previously reported on two patients who were treated with thalidomide for resistant MM and developed EM plasmacytomas in the CNS and skin despite of a good response in the bone marrow [42]. Rosinol et al. [38] from the same Spanish group also reported that none of 11 patients with EM plasmacytomas responded to thalidomide despite a serological response in four of them. The response rate was significantly higher in patients without EM involvement than in patients with such involvement (59% versus 0%). Furthermore, the same authors reported that two patients without EM involvement developed soft tissue plasmacytomas while on thalidomide treatment manifested by retro-orbital and multiple subcutaneous masses and a presternal mass [38]. Anagnostopoulos et al. [43] found that after treatment with thalidomide-containing regimens some patients with MM showed discordant responses of the monoclonal protein levels and the bone marrow or EM plasmacytosis. Alexandrescu et al. [44] reported a patient with extramedullary lesions in the setting of MM treated with thalidomide. The EM progression despite a good medullary and serological response supports the importance of a bone marrow microenvironment-mediated mechanism as the effect of thalidomide in MM [38]. It might be that as previously hypothesized for APL, a change in the expression of certain adhesion molecules on the myeloma and/or the stromal cells is responsible for this phenomenon [42].

As plasmacytomas are heterogeneous in nature there are different observations in other clinical settings. Biagi et al. [45] reported on three patients who underwent allogetic bone marrow transplantation and subsequently relapsed with EM disease, which all responded to thalidomide. These authors postulated that the efficacy of thalidomide on EM involvement after transplant could be different to that in patients who had received only conventional chemotherapy. Similarly, Terpos et al. [46] reported the successful use of thalidomide in three patients with EM relapse post-autologous stem cell transplantation. Thalidomide in combination with dexamethasone and chemotherapy is apparently more effective than thalidomide alone [47].

bortezomib

A new modern treatment of MM is by the proteasome inhibitor bortezomib. Unlike thalidomide, which was mainly associated with EM progression of plasmacytomas, bortezomib has been used successfully in treating EM manifestations of MM.

De Giglio et al. [48] presented the case of a patient with MM who was receiving thalidomide and presented with several hepatic plasmacytomas. The patient then received bortezomib and had a transient response. Patriarca et al. [49] described a patient with MM who developed paraspinal and rib plasmacytomas, as well as cranial nerve palsies without bone marrow involvement or serum or urine paraprotein. The patient responded to bortezomib with resolution of the cerebral MRI and thoracic CT lesions. Paubelle et al. [50] reported a patient with end-stage myeloma and multiple plasmacytomas who failed to respond to chemotherapy and thalidomide but responded completely to bortezomib. These three reports were the first ones on the activity of this promising agent on EM plasmacytomas. Subsequently, Rosinol et al. [51] reported the successful treatment of three out of four patients with extramedullary plasmacytomas with bortezomib, showing that it may be useful in clinical situations of extramedullary disease in which other agents, such as thalidomide, may not be effective.

Bortezomib has extensive tissue penetration; however, data from studies conducted in non-human primates have indicated that bortezomib does not penetrate into the CNS or into various regions of the eye [49].

As this treatment has only recently been introduced, time will tell whether this anti-cancer drug will also adversely affect the development of EMD.

imatinib

As imatinib has become the treatment of choice for CML during the last years, reports of EMD at unusual sites have increasingly appeared.

Breccia et al. [52] were the first ones to report the occurrence of an EM blast crisis manifested by a pleural effusion containing Ph(+) cells in a patient who was treated with imatinib and had obtained a major cytogenetic response. Smaradottir et al. [53] reported on a CML patient who developed an EM blast crisis involving a left inguinal lymph...
node and iliac soft tissue mass. Beyazit et al. [54] reported on two CML patients who developed EM blast crisis during imatinib treatment manifested by mediastinal lymphadenopathy with left pleural effusion and by leptomeningeal blastic infiltration. Rosario Cavalheiro et al. [55] reported on a patient treated for 10 months with imatinib for chronic phase CML who developed EM blast crisis manifested by a large pelvic mass.

Several cases of isolated CNS relapse in patients while in complete bone marrow cytogeneric remission were recently reported. Petzer et al. [56] reported a patient with lymphoid blast crisis who responded excellently to imatinib but developed an isolated CNS relapse. Subsequent analyses of imatinib concentrations in the CSF revealed 2-log lower CSF levels of imatinib than corresponding plasma levels. Bujassoum et al. [57] presented two cases of patients treated with imatinib who achieved complete cytogeneric remission within 3 months and subsequently developed CNS relapses while remaining in complete cytogeneric remission. Borenhauser et al. [58] also reported a patient with lymphoid blast crisis who achieved a complete cytogeneric remission with imatinib but developed an isolated CNS relapse. The levels of imatinib and its metabolite N-desmethyl STI were 40-fold lower in the cerebral spinal fluid than in plasma. Measured CSF levels were below the concentration known to be required for 50% inhibition of the BCR–ABL tyrosine kinase [59]. The poor penetration into the CSF is somewhat surprising as imatinib is a small lipophilic molecule expected to have good penetration into the CSF [56]. A recent study in mice shows that the CNS can become a sanctuary site when animals harboring BCR/ABL stem cells are maintained on imatinib for several months [60].

Interestingly, the levels of imatinib and its metabolite are not elevated in patients with CNS involvement in whom an impairment of the BBB occurs for anti-infectious drugs. Since there is recent evidence for P-glycoprotein-mediated resistance to imatinib, one might speculate that increased efflux from the CSF may be one of the explanations for the low measured levels of imatinib and its metabolite [61]. It is possible that with longer follow-up, more patients with CML achieving molecular remission with imatinib will relapse at unusual sites.

Similar to the other targeted agents, imatinib has also been occasionally successful in treating EMD. Naito et al. [62] described a patient with CML who developed extramedullary blast crisis manifested by lymphadenopathy while treated on interferon. The patient was successfully treated with imatinib 600 mg daily, which led to the complete disappearance of lymphadenopathy within a month and also to major cytogenetic response in the bone marrow. This emphasizes again the ‘Dr Jeckel and Mr Hyde’ double face of the recently introduced targeted therapies.

Table 1. Extramedullary disease (EMD) and targeted therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main EMD sites</th>
<th>Risk factors</th>
<th>Use for EMD treatment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRA</td>
<td>Skin, CNS, ear, lung, pleura, lymph nodes</td>
<td>Prolonged survival, poor penetration into CSF, sanctuary sites, up-regulation of adhesion molecules, leukocytosis, ATRA syndrome, tissue injury</td>
<td>Yes</td>
<td>1–30</td>
</tr>
<tr>
<td>ASO</td>
<td>CNS</td>
<td>Poor penetration into CSF, leukocytosis</td>
<td>Unknown</td>
<td>18, 20, 35, 36</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>CNS, soft tissues, skin</td>
<td>Prolonged survival, dependence on bone marrow microenvironment</td>
<td>Yes (after alloBMT or with chemotherapy)</td>
<td>37–47</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Not described</td>
<td></td>
<td>Yes</td>
<td>48–51</td>
</tr>
<tr>
<td>Imatinib</td>
<td>CNS, pleura, lymph nodes, soft tissues</td>
<td>Prolonged survival, poor penetration into CSF</td>
<td>Yes</td>
<td>52–58, 62</td>
</tr>
</tbody>
</table>

As for the cases of EMD in APL patients treated with ATRA, there is suggestive evidence that ATRA use has increased the incidence of EMD. Again, it could be simply by prolonging the survival of the patients or by poor penetration of the CSF. However, we would suggest a more active role. ATRA could induce expression of adhesion molecules like CD56 that promote extravasation of the leukemic cells and eventually establishment of extramedullary site. This could be enhanced by the ATRA syndrome where ATRA might promote the migration of differentiating blasts into extramedullary tissues forming a reservoir of viable cells that could later proliferate and result in an EM recurrence.

discuss**

As the use of non-chemotherapy targeted treatments is expanding it appears we are faced with the broadening phenomenon of extramedullary progression despite good response in the bone marrow.

A common explanation for the association of extramedullary disease and targeted therapies could be simply life prolongation by these sophisticated treatments allowing for disease progression arising from cells ‘hidden’ in sanctuary sites not accessible to these agents. Another common mechanism is poor penetration into the CSF. Typical examples are the CNS relapses observed with ATRA, ASO, thalidomide and imatinib.

Apparently, all these drugs have a poor penetration of the BBB. This has been documented with imatinib whose concentrations in the CSF are much lower than in the plasma.

Further to these common mechanisms, we assume that there are also particular mechanisms for individual targeted therapies. With thalidomide, another mechanism appears to be the cause of EMD. This agent needs the bone marrow microenvironment to exert its anti-myeloma effect and, therefore, is less effective on EM myeloma cells, allowing for the development of EMD. This is particularly evidenced in conventionally treated patients.

As for the cases of EMD in APL patients treated with ATRA, there is suggestive evidence that ATRA use has increased the incidence of EMD. Again, it could be simply by prolonging the survival of the patients or by poor penetration of the CSF. However, we would suggest a more active role. ATRA could induce expression of adhesion molecules like CD56 that promote extravasation of the leukemic cells and eventually establishment of extramedullary site. This could be enhanced by the ATRA syndrome where ATRA might promote the migration of differentiating blasts into extramedullary tissues forming a reservoir of viable cells that could later proliferate and result in an EM recurrence.
Bortezomib has a good penetration into soft tissues and, in contrast to thalidomide, has a beneficial effect on plasmacytomas and has been successfully used in patients where thalidomide has failed. We therefore suggest that its use will be less associated with EMD. Furthermore, it might be useful in the treatment of EMD. Table 1 summarizes the major sites, the known risk factors and possible mechanisms for the association of EMD and targeted therapies.

Since the use of these sophisticated therapies is broadening, we should be aware of their ‘two-edged sword’ nature and potential to have either a detrimental or a therapeutic effect with respect to EM manifestation in hematological malignancies.

references