Case Reports

ACUTE MYELOID LEUKAEMIA OF MIXED MEGAKARYOCYTIC AND ERYTHROID ORIGIN: A CASE REPORT AND REVIEW OF THE LITERATURE

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Key words: acute myeloid leukaemia, erythroleukaemia, megakaryoblast, multilineage involvement

ABSTRACT

We report the case of a 78-year-old man who presented with acute myeloid leukaemia showing subpopulations of cells expressing platelet-associated markers and the presence of a pan-myeloid component, besides glycophorin A-positive cells. Most of the immature cells had a proerythroblast-like morphology and we classified this case as an FAB-M6 variant, as suggested by Bain (1). According to the WHO classification, this leukaemia fulfilled the criteria of 'AML with multilineage dysplasia' (2). Immunophenotyping characteristics showed two distinct aberrant subpopulations, a young pan-

myeloid (CD45+ with low density, CD34+, CD117+, CD13+, CD33+, partial cytoplasmic myeloperoxidase (MPO)+) population with platelet-associated markers (CD41+, CD42+, CD61+) and a CD45+, CD117+, CD34- population with partial CD235a positivity indicative for erythroid maturation. This case belongs to the group of 'early' erythroblastic leukaemias where a subset of progenitor cells present with erythroid-megakaryocyte bipotentiality or are blocked at an early BFU-E (burst-forming unit erythrocyte)-like stage of erythroid differentiation (11, 12, 13).

INTRODUCTION

We report the case of *de novo* leukaemia showing subpopulations of cells expressing platelet-associated markers and the presence of a pan-myeloid component, besides glycophorin A-positive cells. Recent experimental studies support the hypothesis that during normal haematopoietic development, erythroblasts and megakaryoblasts arise from a common committed progenitor, the BFU E/MK (burst-forming unit erythrocyte megakaryocyte). Consistent with this common origin, erythroid and megakaryocytic gene expression are largely regulated by the same transcriptional regulatory elements, including GATA-1 and NF-E2. Genetic manipulation of either of these transcriptional factors leads to abnormalities in both lineages, supporting this close relationship (3, 4, 5, 6). We reasoned on the base

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of morphologic, immunophenotypic and cytogenetic findings that in this patient a leukaemia had occurred at the progenitor cell level common to both erythroid and megakaryocytic lineages. In the WHO classification, this case is designated as an 'AML with multilineage dysplasia' (2). But this uncommon haematologic malignancy poses difficulties in precise FAB classification (7, 8). On the base of morphologic characteristics we concluded an erythroleukaemia FAB M6 variant, as suggested by Bain (1).

By reviewing the literature this case seems to be a very rare haematologic malignancy presenting with heterogenous clinical and laboratory features. The clinical, morphologic, immunophenotypic, and cytogenetic characteristics are reviewed in this article.

RESULTS (Table 1)

Clinical and laboratory characteristics

A 78-year-old man was admitted to our hospital presenting with complaints of back pain, fatigue and malaise since a month. At presentation his complete blood count showed a leukocyte count of $16.2 \times 10^9/L$

(4.3-10), a haematocrit of 36.0% (40-50), a haemoglobin of 12.5 g/dL (13-17) and a platelet count of $40 \times 10^9/L$ (140-440). Eight per cent circulating immature cells (3% blasts) were noted on the peripheral blood smear. Biochemical findings were LDH 4949 U/L (313-618), D-dimers 2.4 $\mu g/mL$ (0-0.5), iron 58 $\mu g/dL$ (28-180), AST 149 U/L (5-40), ALT 274 U/L (7-56), AF 212 U/L (36-95), GGT 386 U/L (13-45) and CRP 3.4 mg/dL (<0.5).

The diagnosis of AML M6 variant (acute erythroleukaemia) was made based on the bone marrow aspirate findings. Induction chemotherapy consisting of mitoxantrone, cytarabine and etoposide was complicated by cordecompensation, atrial fibrillation and mild acute renal insufficiency. During the period of neutropaenia the patient developed a pneumonic infiltration successfully treated with broad spectrum antibiotics and antifungal agents. Because of good clinical and haematological recovery with normalisation of thrombocyte and leukocyte count in absence of abnormal cells, the patient could leave the hospital after one month.

However, one week later he was hospitalised again with serious back pain, fast atrial fibrillation, fatigue, vertige, confusion and night sweating. Laboratory findings were LDH 1942 U/L, AST 31 U/L, ALT 46 U/L, AF 186 U/L, GGT 213 U/L, CRP 8.9 mg/dL, leukocyte count $18.6 \times 10^9/L$, haematocrit 31.4 %, haemoglobin 10.6 g/dL and a platelet count of $185 \times 10^9/L$. The diagnosis of progressive leukaemia was made and the patient died within 3 months of diagnosis.

Table 1: Summary of results at presentation

Gender	Male
Age	78 years
Symptoms	Back pain, fatigue, malaise
Leukocyte count ($\times 10^9/L$)	16.2 (4.3-10)
Haematocrit (%)	36.0 (40-50)
Haemoglobin (g/dL)	12.5 (13-17)
Platelet count ($\times 10^9/L$)	40 (140-440)
Blasts (% in peripheral blood)	3
Marrow blasts (%)	47.3 morphologically proerythroblast-like cells
Dysplasia	Myeloid cells: 13%; Mature erythroid precursors: 7.9%; Blast cells: 47.3%
Cytochemistry	ANAE-; Peroxidase-; PAS+; sporadic ringed sideroblasts
Immunophenotype subpopulation 1 (29% of the cellularity)	CD45+ low density, CD34+, CD117+, CD13+, CD33+, partial cytoplasmic MPO+, CD11c-, CD235a-, CD41+, CD42+, CD61+, CD7+
Immunophenotype subpopulation 2 (22% of the cellularity)	CD45+ low density, CD34-, CD117+, partial CD235a+
Cytogenetics	MAKA
Treatment	Induction chemotherapy (mitoxantrone, cytarabine, etoposide)
Survival (months)	3

Bone marrow aspirate: Cytological characteristics

At onset, the bone marrow aspirate showed a granulopoiesis (myeloid component: 33.2%) characterised by a mild dysplasia (13%) with mainly neutrophils (24.6%) and a few granulocyte progenitors (myelocytes: 1%, metamyelocytes: 2.6%, neutrophilic bands: 5%). A remarkably rich erythroid component (proerythroblasts: 47.3%, basophilic erythroblasts: 5.3%, polychromatophilic erythroblasts: 2.6%) mainly consisted of blast cells showing a proerythroblast-like aspect. These erythroid blast cells (Figure 1a) were characterized by an abundant deep basophilic cytoplasm with the exception of a zone localized near the nucleus. They showed typical "blebs" as seen in proerythroblasts. The nucleus was round or slightly irregular in shape with fine chromatine distribution and a few with visible nucleolus. These atypical blasts did not contain azurophilic granules. Moreover, mature erythroid precursors (basophilic

Figure 1a: Bone marrow smear shows two atypical proerythroblasts.

Figure 1b: Bone marrow smear shows a binucleated erythroblast.

to acidophilic erythroblasts) were limited in percentage (7.9%) and showed strong dysplasia (Figure 1b). Morphologically no other type of blast could be recognized.

By cytochemical staining these blasts were α -naphthyl acetate esterase (ANAE) negative, peroxidase negative and periodic acid-Schiff (PAS) positive (block-like staining pattern), which confirmed their erythroblast aspect. Sporadically ringed sideroblasts were observed with Perls staining.

In this case, fewer than 30% (20% according to the WHO classification) of non-erythroid cells were blasts and consequently the FAB criteria for AML M6 could not be fulfilled; nevertheless this seemed to be the category where it fitted most naturally. Following the suggestion of Bain (1) we designated an AML M6 variant with criteria for diagnosis being that more than 50% of bone

marrow cells are erythroid and more than 30% are immature erythroid cells resembling proerythroblasts or basophilic erythroblasts (7).

However, the morphological appearance, which showed that most of the immature cells had a proerythroblast-like morphology, was not completely compatible with the immunophenotyping characteristics which we will describe in the next chapter.

Bone marrow aspirate and bone marrow biopsy: Immunophenotyping characteristics

Mononuclear cells were isolated by density gradient separation, after labelling for 15 minutes with monoclonal antibodies, cells were washed and red blood cells were lysed using ammoniumchloride. Data were acquired on a Cytomics FC500 (Beckman Coulter, Fullerton, CA, USA) and analysed using CXP software. For intracellular immunostaining cells were fixed and permeabilized using IntraStain (DakoCytomation, Glostrup, Denmark).

At onset we found the following immunophenotyping characteristics for the bone marrow aspirate. Immunostaining 1 (CD13/CD33/CD34/CD15/CD45) showed a young (CD34+, CD45+ with low density) population accounting for 29% of the cellularity and positive for pan-myeloid markers of differentiation (CD13/CD33) (Figure 2a). Immunostaining 2 (CD235a/CD11c/CD34/CD117/CD45) showed that this CD34+ population was also CD117+, CD11c- and CD235a- (Figure 2b). Other markers expressed on this population were the platelet glycoproteins CD41 (73% within the CD34+ population), CD61 (57% within the CD34+ population) and CD42 (25% within the CD34+ population). The CD34+ population also expressed the T-cell marker CD7 (33% within the CD34+ population) and had cytoplasmic MPO positivity (29% within the CD34+ population). In addition, by using immunostaining 2, a population with a different phenotype was revealed. This population, accounting for 22% of the cellularity, consisted of cells positive for CD45 (low density) and CD117 but negative for CD34. In the dot plot CD45/CD235a (Figure 2b) there was a continuum of CD117+/CD34- cells who gradually lost their CD45 positivity and gained CD235a positivity suggesting the erythroid nature of these cells, which is supported by their proerythroblast-like morphology.

In conclusion, two distinct aberrant subpopulations were observed, a young pan-myeloid (CD45+, CD34+, CD117+, CD13+, CD33+, partial cytoplasmic MPO+)

Figure 2a: Immunostaining 1: CD13-FITC/CD33-PE/CD34-ECD/CD15-PE-Cy5/CD45-PE-Cy7. Colour preference: Red: CD34+/CD45+ low density Blue: CD15+/CD13- Orange: CD15-CD13+ Green: CD34-/CD15-/CD33-/CD45+ low density. Gating strategy: ungated

Figure 2b: Immunostaining 2: CD235a-FITC/CD117-PE/CD34-ECD/CD117-PE-Cy5/CD45-PE-Cy7. Red: CD34+/CD45+ low density Green: CD117+/CD34-/CD45+ low density. Gating strategy: (1) Ungated (2) Gated on CD117+/CD34- (3) Gated on CD117+/CD34+ (4) Ungated

population with platelet-associated markers (CD41+, CD42+, CD61+) and a CD45+, CD117+, CD34-population with partial CD235a positivity indicative for erythroid maturation.

The megakaryocytic differentiation of the first subpopulation was also confirmed by immunohistochemical analysis applied to a fixed, paraffine-embedded bone marrow biopsy. Fifty-seven per cent of all the blasts were positive for factor VIII (Figure 3).

Figure 3: Immunohistochemical stain of blasts on bone marrow biopsy with antibody to factor VIII.

Bone marrow aspirate: Cytogenetics

Cytogenetic analyses (Figure 4) were performed on bone marrow cells cultured in Amniomax (Gibco Invitrogen) for 24 to 48 hours. After harvesting the unstimulated cultures, metaphase spreads were made and G-banding was performed. An attempt was made to analyse at least 20 metaphases, and at least 10 karyotypes were prepared. Karyotypes were designated according to the International System for Human Cytogenetic Nomenclature (2005).

In total, 28 metaphases were found on the cytogenetic preparations. A normal chromosome complement was found in 10 metaphases. In the other 18 metaphases the morphology and the resolution of the banding pattern were subnormal. As a result, karyotyping was hampered. Most of the metaphases showed an at random loss of different chromosomes. A common feature in all the metaphases was the presence of 2 marker chromosomes (= structurally abnormal chromosome in which no part can be identified) and the loss of chromosome 5. In order to identify those marker chromosomes, the fluorescence in situ hybridisation (FISH) technique was applied on the G-banded slide, since this were the only fixed cells available. Unfortu-

Figure 4: Karyotype of abnormal clone

nately, the abnormal metaphases did not show analysable FISH signals. No further characterisation of the marker chromosomes was thus possible. Since chromosome 5 always deletes all the abnormal metaphases, it can be assumed that parts of this chromosome are indeed present in at least 1 of the rearranged marker chromosomes. The cytogenetic abnormalities could be classified as complex (major karyotype aberrations, MAKAs) since they showed ≥ 3 abnormalities (7, 10, 11).

DISCUSSION

Erythroleukaemia (AML M6) seems to be the category in which our case fits most naturally, because the bone marrow morphologically almost exclusively consists of erythroid cells including many very primitive

erythroid cells (47.3% proerythroblast-like cells). Following the suggestion of Bain (1) we designated an AML M6 variant with criteria for diagnosis being more than 50% of bone marrow cells are erythroid and more than 30% are immature erythroid cells resembling proerythroblasts or basophilic erythroblasts (7).

The diagnosis of AML M6, particularly when the cells have a very immature phenotype, may be difficult to distinguish from other types of AML, particularly megakaryoblastic (9), and also from ALL or lymphoma. In our case there was a lack of expression of lymphoid antigens what excluded the latter diagnosis. Distinction from megakaryoblastic leukaemia was more difficult because of the concurrent erythroid-megakaryocytic involvement. The immunophenotyping characteristics revealed 2 distinct aberrant subpopulations, a young pan-myeloid (CD45+, CD34+, CD117+, CD13+, CD33+, partial cytoplasmic MPO+) population (29% of the

cellularity) with platelet-associated markers (CD41+, CD42+, CD61+) and a CD45+, CD117+, CD34- population (22% of the cellularity) with partial CD235a positivity indicative for erythroid maturation. The cytochemical profile (PAS+, ANAE-, peroxidase-) confirmed the erythroblast and megakaryoblast involvement, but could not confirm the partial cytoplasmic MPO positivity found with flow cytometry. Following the WHO this case satisfied the criteria for multilineage involvement (2). In conclusion, the case should be classified as AML with multilineage dysplasia, because there is dysplasia involving $\geq 50\%$ of the cells of at least 2 lines. The myeloid component is characterized by a mild dysplasia (13%). Mature erythroid precursors all showed strong dysplasia (7,9%). Together with the atypical blasts (47,3%), dysplasia is present in 68,2% of the cells. Demonstrated by flow cytometry, some of these blasts showed megakaryocytic involvement, what was also proven by factor VIII positivity. Morphologically no other megakaryocytic forms were found in the bone marrow aspirate.

A review of the literature shows that leukaemias of erythroid lineage represent infrequent haematologic malignancies presenting with heterogenous clinical and laboratory features. 'Early' erythroblastic leukaemias, like our case, where a subset of progenitor cells present with erythroid-megakaryocyte bipotentiality or are blocked at an early BFU-E (burst-forming unit erythrocyte)-like stage of erythroid differentiation and not morphologically identifiable by the usual criteria, are very uncommon diseases. They may arise as *de novo* AML, in Down's syndrome, as therapy-related AML or as blast crisis in CML (11, 12, 13).

In the literature (Table 2) we found 11 paediatric cases of 'early' erythroblast leukaemia, whereas 2 *de novo* leukaemias associated with MAKa (10), 5 cases

associated with trisomy 21 (13, 14), 3 cases with isolated chromosomal abnormality appearance (1 case with t(1;22), 1 with inv(6)(p22;q22) and 1 with del(5q)) (13, 15) and one congenital case without chromosomal abnormality (5). We found 10 adult cases of *de novo* 'early' erythroblast leukaemias, all associated with MAKa (11, 12, 13, 16) and, as in our case, associated with a short median survival. Although MAKa were observed in all these *de novo* 'early' erythroblast leukaemias, complex karyotypes have also been found in other MDS and AML, possibly reflecting exposure to myelotoxic agents (11).

The reason for the low incidence of erythroleukaemia could be due to the fact that glycophorin A detected by monoclonal antibodies (McAbs) is not a sufficiently early marker of erythroid differentiation (12). This molecule is considered to be a very specific but rather late erythroid marker (13). Indeed, Glycophorin A detected by these McAbs is not expressed on the membrane of erythroid progenitors, i.e., CFU-E (colony-forming unit erythrocyte) and BFU-E (burst-forming unit erythrocyte). Although not specific, CD71 (the transferrin receptor) is present on the earliest recognizable erythroid cells and its reactivity is suggestive of erythroid differentiation since it is rarely present in other myeloid leukaemias (10). Another not specific marker is the CD36 marker, which usually detects erythroid progenitors at earlier stages of differentiation and is characteristically positive in acute megakaryoblastic leukaemias. Other McAbs that recognize antigens and that are expressed before GPA during normal erythropoiesis are anti-carbonic anhydrase I (CAI) and FA6-152 McAbs (12). Unfortunately we did not apply these markers in one of our immunostainings, which could maybe prove the erythroid involvement of the CD34+ cells and the partial erythroid maturation from these CD34+ cells.

Table 2: Review of the literature

Cases 'early' erythroblast leukaemia	Cytogenetics
2 paediatric cases (10)	<i>De novo</i> leukaemias associated with MAKa
5 paediatric cases (13, 14)	Trisomy 21
3 paediatric cases (13, 15)	Isolated chromosomal abnormality appearance (t(1;22) ; inv(6)(p22;q22) ; del(5q))
1 paediatric case (5)	Congenital case without chromosomal abnormality
10 adult cases (11, 12, 13, 16)	<i>De novo</i> leukaemias associated with MAKa

CONCLUSION

This case is an example of acute myeloid leukaemia of mixed megakaryocytic and erythroid origin. We were confronted with the difficulties in classifying this leukaemia with multilineage involvement. According to the morphologic characteristics this case was classified as an FAB M6 variant, as suggested by Bain (1). In the WHO classification, cases of AML assigned to FAB M6 category fall into various categories. Most are designated 'AML with multilineage dysplasia' and 'acute erythroid leukaemia' (1). Our case fulfilled the first designation.

ABSTRACT

We beschrijven de casus van een 78-jarige man die zich presenteerde met een acute myeloïde leukemie gekenmerkt door subpopulaties van cellen met expressie van plaatjes geassocieerde en pan-myeloïde markers, naast glycophorine A-positieve cellen. Meeste van deze immature cellen hadden een proerythroblasten morfologie en we klasseerden deze casus als een FAB-M6 variant, voorgesteld door Bain (1). Volgens de WHO klassificatie, voldoet deze leukemie aan de criteria van 'AML met multilineage dysplasia' (2). Immunofenotypering toont twee distinct aberrante subpopulaties, een jonge pan-myeloïde (CD45+ met lage densiteit, CD34+, CD117+, CD13+, CD33+, partiële cytoplasmatische myeloperoxidase (MPO)+) populatie met plaatjes geassocieerde markers (CD41+, CD42+, CD61+) en een CD45+, CD117+, CD34- populatie met partiële CD235a positiviteit indicatief voor erythroïde maturatie. Deze casus behoort tot de groep van 'vroeg' erythroblast leukemieën waarbij een subset van progenitor cellen een erythroïd-megakaryocytaire bipotentialeiteit vertonen of geblokkeerd zijn bij een vroege BFU-E (burst-forming unit erythrocyte) stadium van erythroïde differentiatie (11, 12, 13).

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Augmentin Retard wordt bij het begin van de maaltijd ingenomen. De tabletten worden zonder kauwen geslikt, bij voorkeur met water. **Contra-indicaties:** Overgevoeligheid voor bèta-lactamantibiotica (kruisallergie penicillines-cefalosporines) of voor één van de hulpstoffen. Mononucleosis infectiosa en acute lymfatische leukemie (erytheem). Augmentin Retard mag niet worden voorgeschreven aan patiënten die leverfunctiestoornissen of icterus zouden hebben vertoond naar aanleiding van eerder gebruik van een vorm van Augmentin. **Bijwerkingen:** Er werden gegevens gebruikt afkomstig van grote klinische studies om de frequentie te bepalen van zeer vaak voorkomende tot zeldzame bijwerkingen. De frequentie die werd toegekend aan andere bijwerkingen werd hoofdzakelijk bepaald op basis van postmarketing ervaring en verwijst bijgevolg eerder naar het percentage gemelde voorvallen dan naar de werkelijke frequentie. De volgende conventie werd gebruikt om de frequentie te definiëren: zeer vaak ($>1/10$), vaak ($>1/100$ en $<1/10$), soms ($>1/1000$ en $<1/100$), zelden ($>1/10000$ en $<1/1000$), zeer zelden ($<1/10000$). **Infecties:** Vaak: genitale candidose, candidiasis van huid en slijmvliezen. **Bloed- en lymfestelselaandoeningen:** Zelden: reversibele leukopenie (inbegrepen neutropenie) en reversibele trombocytopenie. Zeer zelden: reversibele agranulocytose en hemolytische anemie. Verlengde bloedingstijd en protrombintijd. **Immuunsysteemaandoeningen:** Zeer zelden: oedeem van Quincke, anafylaxis, serumziekte, overgevoeligheidsvasculitis. **Zenuwstelselaandoeningen:** Soms: duizeligheid, hoofdpijn. Zeer zelden: reversibele hyperactiviteit, convulsies. **Maagdarmstelselaandoeningen:** Zeer vaak: diarree. Vaak: nausea, buikpijn. Soms: braken, indigestie. Zeer zelden: antibioticagebonden colitiden (colitis pseudomembranosa en hemorrhagische colitis inbegrepen). **Lever- en gelaandoeningen:** Soms: een matige stijging van de serumtransaminasen (AST en/of ALT) (bij patiënten die worden behandeld met bèta-lactamantibiotica), maar de betekenis van deze waarnemingen is niet gekend. Zeer zelden: hepatitis en cholestatiche icterus. Deze voorvallen werden waargenomen met andere penicillines en cefalosporines. De leveraantastingen die werden gemeld bij patiënten die Augmentin namen, treffen vooral mannen en oudere patiënten en zouden gebonden zijn aan een verlengde behandeling. De tekenen en symptomen van leveraantasting treden doorgaans op tijdens de behandeling of kort na stopzetting daarvan. In bepaalde gevallen echter treden ze meerdere weken na het stoppen van de behandeling op. De leveraantastingen zijn doorgaans omkeerbaar maar ze kunnen ernstiger zijn en zeer zelden werd overlijden waargenomen. Dit deed zich nagenoeg altijd voor bij patiënten met ernstige onderliggende aandoeningen of die geneesmiddelen namen die gekend zijn voor hun bijwerkingen op de lever. **Huid- en onderhuidaandoeningen:** Vaak: erytheem (zogenoemd van de 5de dag) (zoals voor amoxicilline komt zogenaamd « 5de dag » erytheem voor bij 2 % van de met Augmentin behandelde patiënten). De incidentie ligt hoger bij patiënten met mononucleosis infectiosa of lymfoïde leukemie. Soms: rash, pruritus, urticaria. Zelden: erythema multiforme. Zeer zelden: syndroom van Stevens-Johnson, syndroom van Lyell, bullieuze exfoliatieve dermatitis, acute veralgemeende exanthemateuze pustulosis. Als zich een overgevoeligheidsreactie voordoet, moet de behandeling gestopt worden. **Nier- en urinewegaandoeningen:** Zeer zelden: interstitiële nefritis, cristallurie. **Houder van de vergunning voor het in de handel brengen:** GlaxoSmithKline s.a./n.v., rue du Tilleul 13, 1332 GENVAL. **Nummer van de vergunning voor het in de handel brengen:** 725 IS488 F3. **Datum van herziening van de tekst:** A. Datum van de laatste herziening van de samenvatting van de productkenmerken: 19/04/2004 (SPK8). B. Datum van de laatste goedkeuring van de samenvatting van de productkenmerken: 10/05/2004. **Afleveringswijze:** Geneesmiddel op medisch voorschrift.

PP: 476,67 €***
1 flacon 5 mg/100 ml

70%

réduction du
risque* de fractures
vertébrales¹

($p < 0.001$)

41%

réduction du
risque* de fractures
de la hanche¹

($p = 0.0032$)

25%

réduction du risque* de fractures non vertébrales^{1, **}

($p < 0.001$)

Dénomination : Aclasta 5 mg solution pour perfusion **Composition et forme** : Chaque flacon de 100 ml de solution contient 5 mg d'acide zolédronique anhydre, correspondant à 5,330 mg d'acide zolédronique monohydraté. Un ml de solution contient 0,05 mg d'acide zolédronique anhydre correspondant à 0,0533 mg d'acide zolédronique monohydraté. **Indications** : Traitement de l'ostéoporose post-ménopausique chez les patientes à risque élevé de fractures. Traitement de la maladie de Paget. **Posologie** : Pour le traitement de l'ostéoporose post-ménopausique, la dose recommandée est une perfusion intraveineuse de 5 mg d'Aclasta, administrée une fois par an. Pour la maladie de Paget, Aclasta doit uniquement être prescrit par des médecins expérimentés dans le traitement de cette pathologie. La dose recommandée est une unique perfusion intraveineuse de 5 mg d'Aclasta. Répétition du traitement de la maladie de Paget : aucune donnée spécifique n'est disponible concernant un traitement répété. Il a été observé une période de rémission prolongée chez les patients répondeurs au traitement de la maladie de Paget après une unique administration d'Aclasta. Aclasta (5 mg/100 ml, solution pour perfusion prête à l'emploi) est administré par l'intermédiaire d'un dispositif de perfusion, avec prise d'air et à vitesse de perfusion constante. La durée de la perfusion ne doit pas être inférieure à 15 minutes. Les patients doivent être correctement hydratés avant l'administration d'Aclasta. Cela est particulièrement important pour les patients âgés et les patients qui reçoivent un traitement diurétique. Un apport adapté en calcium et vitamine D est recommandé simultanément à l'administration d'Aclasta. De plus, chez les patients atteints de la maladie de Paget, il est fortement conseillé d'administrer une supplémentation adaptée en calcium correspondant à un apport en calcium-élément d'au moins 500 mg deux fois par jour, pendant au moins les 10 jours suivant l'administration d'Aclasta. L'incidence des effets indésirables survenant dans les trois premiers jours suivant l'administration d'Aclasta peut être diminuée en administrant du paracétamol ou de l'ibuprofène après l'administration d'Aclasta. **Patients insuffisants rénaux** : L'utilisation d'Aclasta n'est pas recommandée chez les patients dont la clairance de la créatinine est < 40 ml/min en raison d'une expérience clinique limitée dans cette population. Aucun ajustement de la dose n'est nécessaire chez les patients dont la clairance de la créatinine est ≥ 40 ml/min. **Patients insuffisants hépatiques** : Aucun ajustement de la dose n'est nécessaire. **Patients âgés (≥ 65 ans)** : Aucun ajustement de la dose n'est nécessaire puisque la biodisponibilité, la distribution et l'élimination ont été similaires chez les patients âgés et chez les patients plus jeunes. **Enfants et adolescents** : Aclasta ne doit pas être utilisé chez l'enfant en dessous de 18 ans compte tenu de l'absence de données concernant la sécurité et l'efficacité. **Contre-indications** : Hypersensibilité à la substance active ou à l'un des excipients ou à d'autres bisphosphonates. Aclasta est contre-indiqué chez les patients ayant une hypocalcémie. Aclasta est contre-indiqué chez la femme enceinte ou qui allaite. **Effets indésirables** : Le pourcentage global de patients qui ont présenté des symptômes survenant après l'administration était de respectivement 44,7 %, 16,7 % et 10,2 % après la première, deuxième et troisième perfusion respectivement. L'incidence individuelle de ces symptômes après la première administration était : fièvre (17,1 %), myalgie (7,8 %), syndrome pseudo-grippal (6,7 %), arthralgie (4,8 %) et céphalée (5,1 %). L'incidence de ces symptômes a diminué nettement avec les doses successives d'Aclasta. La majorité de ces symptômes est survenue dans les trois premiers jours suivant l'administration d'Aclasta, a été d'intensité légère à modérée et a disparu dans les trois jours suivant leur survenue. L'incidence des symptômes survenant dans les trois premiers jours suivant l'administration d'Aclasta peut être diminuée en administrant du paracétamol ou de l'ibuprofène peu après l'administration d'Aclasta. L'incidence globale des fibrillations auriculaires était de 2,5 % (96 des 3 862) et de 1,9 % (75 des 3 852) chez les patients recevant respectivement Aclasta et le placebo. Le taux de fibrillations auriculaires classé comme événements indésirables graves était de 1,3 % (51 sur 3 862) chez les patientes traitées par Aclasta comparé à 0,6 % (22 sur 3 852) chez les patientes recevant le placebo. Le mécanisme de l'augmentation de cette incidence des fibrillations auriculaires n'est pas connu. Les effets indésirables très fréquents ($\geq 1/10$), fréquents ($\geq 1/100$, < 1/10), peu fréquents ($\geq 1/1\ 000$, < 1/100) et rares ($\geq 1/10\ 000$, < 1/1 000) sont présentés dans le Tableau 1. Au sein de chaque fréquence de groupe, les effets indésirables sont présentés suivant un ordre décroissant de gravité.

Affections cardiaques	Fréquent	Fibrillation auriculaire
Affections du système nerveux	Fréquent Peu fréquent	Céphalées, vertiges Léthargie, paresthésies, somnolence, tremblements, syncope, dysgueusie
Affections oculaires	Peu fréquent Rare	Conjonctivite, douleur oculaire, uvéite Episcérite, iritis
Affections de l'oreille et du labyrinthe	Peu fréquent	Vertiges
Affections gastro-intestinales	Fréquent Peu fréquent	Nausées, vomissements, diarrhée Dyspepsie, douleur abdominale, sécheresse buccale, oesophagite
Affections du rein et des voies urinaires	Peu fréquent	Augmentation de la créatinémie
Affections de la peau et du tissu sous-cutané	Peu fréquent	Eruption cutanée
Affections musculo-squelettiques et systémiques	Fréquent Peu fréquent	Myalgies, arthralgies, douleurs osseuses, douleurs rachidiennes, douleurs au niveau des extrémités Gonflement articulaire, douleurs de l'épaule, spasmes musculaires, faiblesse musculaire, raideur articulaire
Troubles du métabolisme et de la nutrition	Fréquent Peu fréquent	Hypocalcémie ¹ Anorexie
Troubles généraux et anomalies au site d'administration	Très fréquent Fréquent Peu fréquent	Fièvre Syndrome pseudo-grippal, frissons, fatigue, asthénie, douleurs, malaise, rigidité ¹ Œdème périphérique, soif
Affections psychiatriques	Peu fréquent	Insomnie

¹ Fréquent en cas de maladie de Paget uniquement. Pour l'hypocalcémie voir ci-dessous.

Ostéonécrose de la mâchoire : Des cas d'ostéonécrose (principalement de la mâchoire) ont été peu fréquemment rapportés, principalement chez des patients atteints d'un cancer et traités par bisphosphonates, dont l'acide zolédronique. Beaucoup d'entre eux présentaient des signes d'infection locale y compris une ostéomyélite. La majorité des cas concerne des patients atteints d'un cancer et ayant subi une extraction dentaire ou d'autres chirurgies dentaires. L'ostéonécrose de la mâchoire présente de multiples facteurs de risque bien documentés incluant le diagnostic d'un cancer, les traitements associés (par exemple : chimiothérapie, radiothérapie, corticothérapie) et des affections associées (par exemple : anémie, troubles de la coagulation, infection, maladie buccale préexistante). Bien que la causalité ne puisse être établie, il est prudent d'éviter une chirurgie dentaire dont la guérison pourrait être retardée. Au cours d'une vaste étude clinique réalisée chez 7 736 patientes, une ostéonécrose de la mâchoire a été observée chez une patiente traitée par Aclasta et chez une patiente traitée par le placebo. Dans les deux cas, l'évolution a été favorable. **Titulaire et numéro d'enregistrement** : Novartis Europharm Limited, Wimblehurst Road, Horsham, West Sussex, H12 5AB, Royaume-Uni. EU/1/05/308/001. **Délivrance** : Prescription médicale. **Dernière mise à jour de la notice** : 3.10.2007

* En comparaison au placebo. ** Les fractures non vertébrales incluent les poignets, les côtes, les bras, les épaules ou les fractures de la hanche; les doigts, les orteils ou les fractures du crâne facial sont exclus. *** Remboursable pour le traitement de la maladie de Paget. 1. Black DM, et al. *New England Journal of Medicine*. 2007;356:1809-22. 2. Aclasta est indiqué dans le traitement de la maladie de Paget et dans le traitement de l'ostéoporose post-ménopausique chez les patientes à risque élevé de fractures. 3. Aclasta SmPC. Novartis Pharma AG.

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