Alemtuzumab causes significant, transient, post-infusion thrombocytopenia and other non autoimmune cytopenias following initial and subsequent courses DX46

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Abstract

Background: Immediate lymphocytopenia is a direct anti-CD52-mediated effect, and delayed autoimmune cytopenias have occurred during immune reconstitution post alemtuzumab (ALE), usually immune thrombocytopenia. However, other immediate post-infusion (PI) cytopenias have not been described. Phase II/III protocols did not examine or report immediate post-infusion hematological parameters.
Objectives: Report PI, transient cytopenias (thrombo-cytopenia [TP] and monocytopenia) associated with ALE.
Methods: Hemograms (CBC) from ALE-treated MS patients from phase I trial of ALE in MS. 1 to 7 courses of CBC data were reviewed. An immediate PI CBC, at end of last infusion in each course, was collected. TP was classified graded as gr I (75K-150K/μL), gr II (50-75K/μL), gr III (25-50K/μL), and gr IV (<25K/μL). Follow up CBC were performed at 4 weeks.
Results: PI thrombocyte counts decline mean 84-88K/μL with courses 1-2 with about 15% of courses having PI thrombocytes less than 100K/μL. Gr I-II TP occurred in 34% (18/53) of first infusion courses and recovered by 4 weeks in 89% (16/18) of cases. Two subjects with mild baseline gr I TP experienced PI gr II transient TP (58 and 63K/μL) and recovered to baseline gr I TP (~140K) at 4 weeks. The second course had 20% (11/56) prevalence of gr I PI TP, with 2/11 still gr I TP at follow up. With courses 3-4, decline means were 61-66K/μL. Decreases in thrombocytes were slightly greater in those developing TP. Third and fourth courses showed 15% (9/59) gr I PI TP afterwards and no TP occurred with the 5th, 6th or 7th infusion in any courses (0/22). Immediate PI monocytopenia occurred uniformly declining from mean 0.5/μL baseline to 0.1/μL immediate PI and recovered by 4 weeks with each course.. Neutropenia did not occur PI; instead, neutrophilia was often present. Profound gr 4 lymphopenia was virtually always present.
Conclusion: Clinically silent TP occurs post ALE, usually mild gr I, short-lived, and presumably not due to a direct anti-CD52 action, as thrombocytes lack CD52 antigen, but do not have Fc receptors. TP at first course indicates it cannot be a delayed autoimmune TP. Decrease of thrombocytes and monocytes occur immediately PI, without evidence for clinical adverse events. PI TP may be an immune complex phenomenon (similar to that seen in rheumatic disease), and likely recover as ALE is eliminated and bone marrow responds. Transient gr I-II PI TP occurs in up to one-third of courses, slightly greater at the initial course, and the greatest degree of PI TP occurs in those with mild preexisting TP. In a small fraction of cases, the decrease in platelets could elevate risk of hemorrhage, especially if qualitative platelet defects happen to be present. Monocytopenia most likely reflects this same phenomenon and may also be in part a direct anti-CD52 cytotoxicity.
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Protocol

- **Phase I retrospective and prospective:**
  NCT01624714: clinicaltrials.gov
- **Inclusion Criteria**
  - **ALE-experienced Inclusion criteria**
    - Off-label treated, refractory, MS clinic cohort, MS with documented relapses
    - Prior treatment experience with approved disease modifying agents
    - ≥1 cycles of prior ALE therapy
  - **ALE-naive Inclusion criteria**
    - Prior treatment experience 1 or more DMTs, refractory, MS clinic cohort, MS with documented relapses
    - Prior treatment experience with approved disease modifying agents
- **Exclusion:** pregnancy, neoplasm, infection, uncontrolled autoimmunity

Alemtuzumab total 60mg first course slow i.v. over 3-5 days. Repeat yearly course total 30-36 mg annually divided over 3 days. In each course 3 days i.v. methyl-prednisolone 1 g were given. Pretreatment with acetaminophen, hydroxyzine, and ranitidine or equivalent were used.

Second course at 12 months. Other courses as indicated.

Background

Post-infusion Cytopenias with ALE occur in other lineages than lymphocytes

- Occur with high dose alemtuzumab for CLL
- Can present a confusing situation since autoimmunity may be feared.
- Cytopenia could conceivably present a safety issue.

We describe the prevalence and extent of immediate post-infusion (PI) hematological changes.

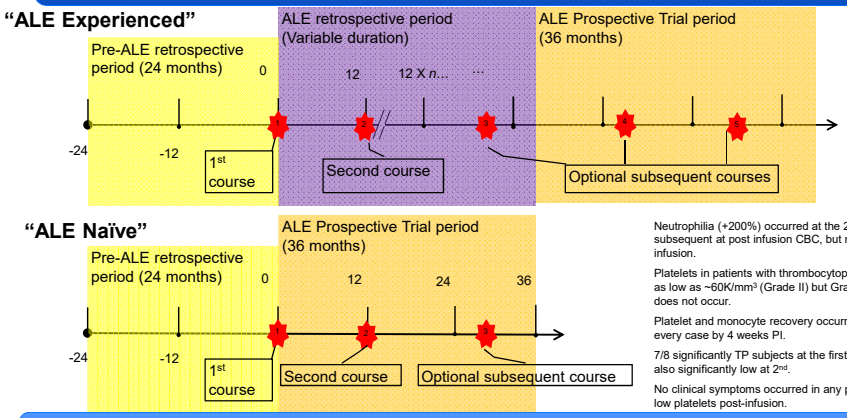
This data was not collected in phase II/III trials

Significant thrombocytopenia can occur.

Study Cohort

Patients:	61 subjects, 41 female, 20 male >= 12 months post ALE, Previously documented relapses
Age at First ALE Infusion:	Mean 49 years, range 33-69 years
Infusion Courses analyzed:	184 Courses analyzed of total 206 courses in up to 7 courses of ALE 1-2 courses 61 subjects 3-4 courses 37 subjects 5+ courses 14 subjects
Follow-up (years):	4.7 (1.4-11.6) Experienced 7.2 (3.2-11.6) Naïve 2.1 (1.4-3.1)
Prior therapies	1 DMT: 8 subjects 2 DMT 19 subjects 3+ DMT 34 subjects
Prior Treatment Experience (within two years)	0 Cyclophosphamide 2 Dimethylfumarate 14 Fingolimod 5 Glatiramer 34 Interferon-beta 2 Leflunomide/Teriflunomide 2 Methotrexate 1 Mitoxantrone 0 Mycophenylate 29 Natalizumab 2 Regular MP, DXM
Prior Treatment Experience entire history	2 Cyclophosphamide 2 Dimethylfumarate 17 Fingolimod 21 Glatiramer 61 Interferon-beta 5 Leflunomide/Teriflunomide 3 Methotrexate 5 Mitoxantrone 3 Mycophenylate 29 Natalizumab 4 Regular MP, DXM 1 Other cytotoxic agents

Trial Design and Results



Neutrophilia (+200%) occurred at the 2nd and subsequent at post infusion CBC, but not the first infusion.

Platelets in patients with thrombocytopenia decline as low as ~60K/mm³ (Grade II) but Grade III/IV TP does not occur.

Platelet and monocyte recovery occurred in nearly every case by 4 weeks PI.

7/8 significantly TP subjects at the first course were also significantly low at 2nd.

No clinical symptoms occurred in any patients with low platelets post-infusion.

Hematological changes after ALE (Post infusion)

	Platelet				Monocyte		Lymphocyte		Neutrophil
ALE Course	Platelets change PI K/mm³	Platelets PI % change	Grade I-II Thrombo-Cytopenia PI <150K/mm³ (%)	Significant thrombo-cytopenia PI <100K/mm³	Monocyte Change PI K/mm³ (n)	Monocyte % change PI	Lymph change PI K/mm³ (n)	Lymph %	Neutropenia at 4 weeks <1.4X103/mm3 (%)
1	-71	-29%	18/50 (36%)	7/50 (14%)	-0.67 (49)	-76%	-1.7(50)	-96%	3/50 (6%)
2	-55	-21%	11/58 (19%)	8/58 (14%)	-0.35 (56)	-73%	-1.1(56)	-92%	2/56 (4%)
3	-66	-25%	7/26 (26.9%)	2/26 (8%)	-0.35 (32)	-46%	-1.1(32)	-91%	0/26 (0%)
4	-61	-25%	2/17 (11.8%)	1/17 (6%)	-0.33 (26)	-62%	-0.99(26)	-77%	0
5+	-49	-19%	0/21 (0%)	0/21 (0%)	-0.40 (21)	-79%	-0.79(21)	-75%	0
1-7	-52	-24%	38/172 (28%)	18/172 (13%)	-0.44 (184)	-68%	-0.85(185)	-89%	0

Conclusions/References

- Post-ALE infusion platelets nearly always decline significantly especially at 1st course, often abnormal, as low as 80K/mm³, without any symptoms in our cohort, and recover virtually always spontaneously by 4 weeks post-infusion.
- A comorbid qualitative platelet defect could place some patients at risk of bleeding. Thrombocytopenia is less beyond the second course.
- Monocytes may decline significantly, and this could represent a transient increased infection risk.
- Neutropenia is rare immediately post-infusion, but occurs sometimes at 4 weeks.
- A repeat study for significant abnormalities after 1-2 weeks or if symptomatic seems wise.
- The findings do not likely represent autoimmunity but rather effect of transient circulation of anti-CD52.

Mechanism of action for platelet destruction may be Fc receptor mediated due to platelet solubilization of immune complexes, given low platelet CD52 expression.

Destruction of monocytes, as with other mononuclear cells, is likely mediated by anti-CD52.

Variable responses in neutrophils may be due to multiple mechanisms (e.g. steroids, anti-CD52, immune complex).

The principal importance of these findings is to avoid confusion of transient effects with autoimmune cytopenia.

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