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Kazakhstan Cancer Society

EHA-KCS Hematology Tutorial on Lymphoma and Multiple Myeloma

Tutored Clinical Case

Speaker:
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Almaty, Kazakhstan
March 14-16, 2019

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Disclosures:

No relevant conflicts of interest to declare

Clinical history

- A 81-year-old woman presented with fatigue and progressively increasing symptoms of anaemia
- Her medical history included only chronic bronchitis; family history didn't include any malignancy
- Performance status: ECOG 3
- Physical examination revealed marked splenomegaly, about 15 cm below the left costal margin, no palpable lymphadenopathy.

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Clinical history

- At the onset of the disease laboratory evaluation revealed cytopenia:
  - Hb 78 g/l (NR 130-180), MCV 120 fl (NR 76-96)
  - WBC 3.4 x 10^9/l (NR 4-11)
  - Platelet count 178 x 10^9/l (NR 150-400)
- Biochemistry report:
  - Total bilirubin 29.5 µmol/l (NR< 22) with direct bilirubin 10.0 µmol/l (NR 0.0-5.0)
  - Serum B12 concentration 135 pg/ml (NR 180-900)

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Clinical history

- The first diagnosis made was pernicious anemia
- The patient received a course of an antianaemic therapy (vitamin B12)
- Haemoglobin concentration increased to 90 g/l

No reticulocyte count

No attention to the possibility of a ‘proliferative syndrome’

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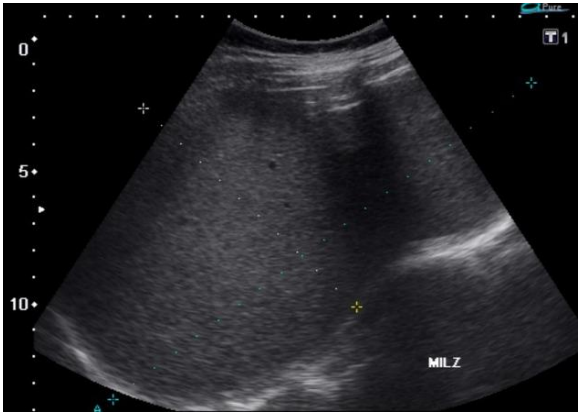
Clinical history



- An ultrasound scan of the abdomen demonstrated markedly enlarged spleen, 23 cm in length An ultrasound scan showed also diffuse minor enlargement of lymph nodes: axillary – right 8.5 mm, left 14 mm, inguinal : right 4.5 mm, left 9.7 mm
- Computed tomography of the chest, abdomen and pelvis confirmed massive splenomegaly

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Clinical history

- But the second diagnosis made was hepatic cirrhosis with massive splenomegaly and hypersplenism as a complication
- In the next 3 months the patient's condition deteriorated: she lost 15 kg in weight, the Hb fell to 57 g/l, total bilirubin rose to 150 µmol/l and indirect bilirubin to 139 µmol/l
- Treatment with blood transfusions resulted in temporary improvement
- Anaemia, haemolysis, a 'proliferative syndrome', significant weight loss could not be related to one disorder

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Clinical history

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Diagnosis

- Complete blood count revealed :
  - Hb 42 g/l, MCV 120 FL
  - WBC 5.3 x 10^9/l
  - The white blood cell differential was 2.7 x 10^9/l neutrophils, 2.2 x 10^9/l lymphocytes, 0.4 x 10^9/l monocytes. No atypical lymphoid forms were noted in the peripheral film
  - Platelet count 231 x 10^9/l (150-400)
  - Reticulocyte count 5.4 % (0.2-2)

  - Other laboratory data:
  - Total bilirubin 194.5 µmol/l (< 22) with indirect bilirubin 170.0 µmol/l
  - Lactate Dehydrogenase (LDH) 1200 iu/l (81-234)
  - Coombs positive

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Diagnosis

- A bone marrow aspirate was hypocellular, with an insignificant increase of lymphocytes – 15%
- Flow cytometry: there was a clonal B-lymphoproliferative disorder with positive markers: CD5, CD23, CD19, CD22, $CD20^{strong}$, HLA-DR, CD200, FMC7. Negative markers: CD25, CD34, CD38, CD43, CD10, CD103.

- The immunophenotype required exclusion of a number of B-cell lymphoproliferative processes, such as chronic lymphocytic leukemia, mantle cell lymphoma and others.

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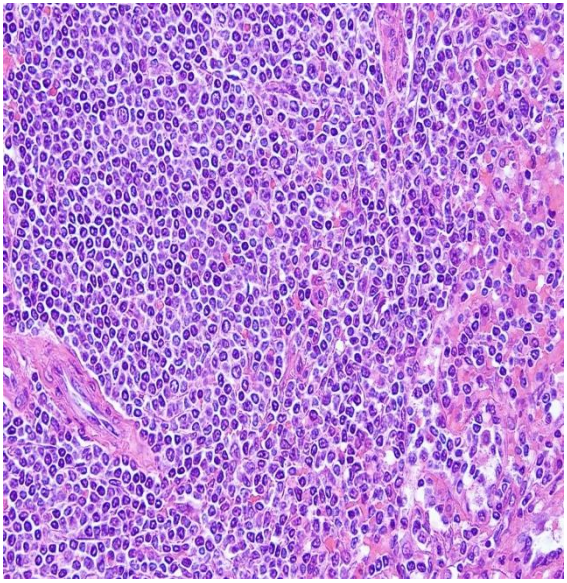
Diagnosis



Bone marrow histology: the marrow was hypercellular with diffuse replacement of normal marrow elements with a micronodular, interstitial and paratrabecular infiltrate of small to medium-sized lymphoid cells with moderate amounts of cytoplasm.

- Immunohistochemistry: infiltration by CD20-positive cells, Cyclin D1/BCL1 not expressed. Low grade B-cell lymphoma, compatible with splenic marginal lymphoma.

Diagnosis

The clinical diagnosis was:

Splenic marginal zone lymphoma (SMZL), complicated by autoimmune haemolytic anaemia (AIHA).

Diagnosis

Diagnosis of SMZL was made by the presence the following features:

- massive splenomegaly, no palpable peripheral lymphadenopathy,
- micronodular, interstitial and paratrabecular infiltration by lymphoid cells on marrow biopsy,
- appropriate positive and negative immunophenotypic features
- presence of AIHA.

The diagnosis of AIHA was based on full blood count (severe macrocytic anaemia), increase of haemolytic parameters (reticulocyte count, lactate dehydrogenase level, hyperbilirubinaemia) in combination with positive Coombs.

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Discussion

AIHA is reported as a potential risk factor of poor outcome for SMZL patients.

Other clinical features associated with a worse outcome:

- The development of lymphadenopathy,
- non-haematopoietic site involvement,
- leukocyte count >20 × 10^9/l,
- lymphocytosis >9 × 10^9/l,
- lymphopenia, anaemia,
- thrombocytopenia,
- use of chemotherapy,
- monoclonal component,
- ECOG ≥2,
- advanced age,
- diffuse pattern of bone marrow infiltration and histological transformation.

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Discussion

In the case of our patient negative prognostic factors are:

- aged ≥80 years
- ECOG 3
- AIHA

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Discussion

- What about the treatment?

Difficulties:

- Age
- Comorbidity
- Haemolysis

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Discussion

ABHH Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular

Revista Brasileira de Hematologia e Hemoterapia
Brazilian Journal of Hematology and Hemotherapy

www.rbhh.org

Review article

Splenic marginal zone lymphoma: a literature review of diagnostic and therapeutic challenges

*Tayse Silva dos Santos, Renato Sampaio Tavares, Danielle Leão Cordeiro de Farias**

Hospital das Clínicas, Universidade Federal de Goiás (UFG), Goiânia, GO, Brazil

Table 2 – Criteria to indicate treatment of splenic marginal zone lymphoma.

Progressive or symptomatic splenomegaly
Cytopenias:
Hemoglobin < 10 g/dL or
Neutrophils < 1×10^9/L
Progressive thrombocytopenia
Constitutional symptoms
Progressive nodal disease
Autoimmune hemolytic anemia

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NCCN Guidelines Version 1.2019
Splenic Marginal Zone Lymphoma

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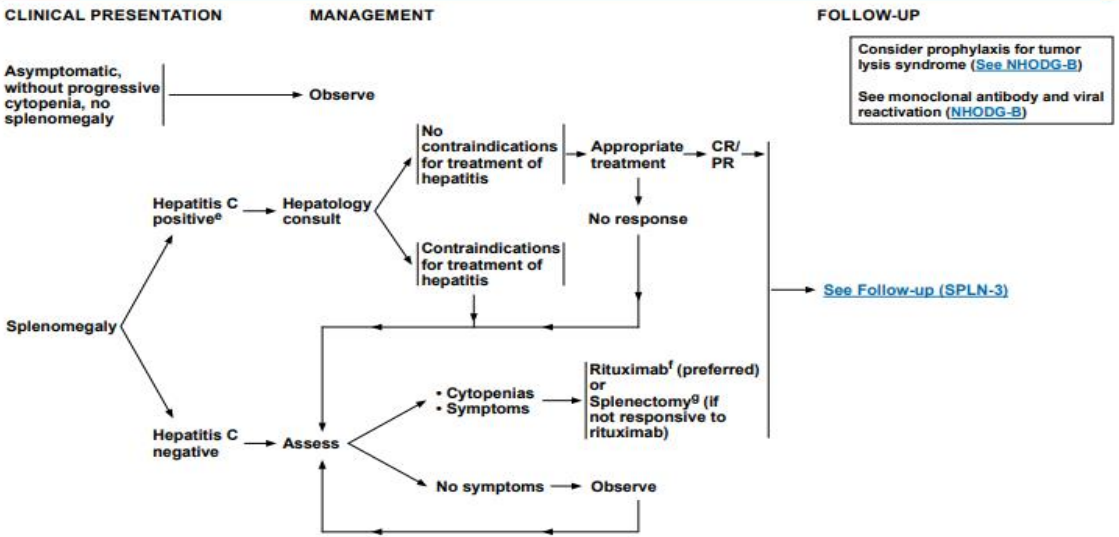

[e]If there is hepatic involvement and hepatitis C positive, treat with an appropriate regimen for hepatitis C.
[f]Tsimberidou AM, Catovsky D, Schlette E, et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer 2006;107:125-135.
[g]Pneumococcal, meningococcal, and hepatitis B vaccinations should be given at least 2 weeks before splenectomy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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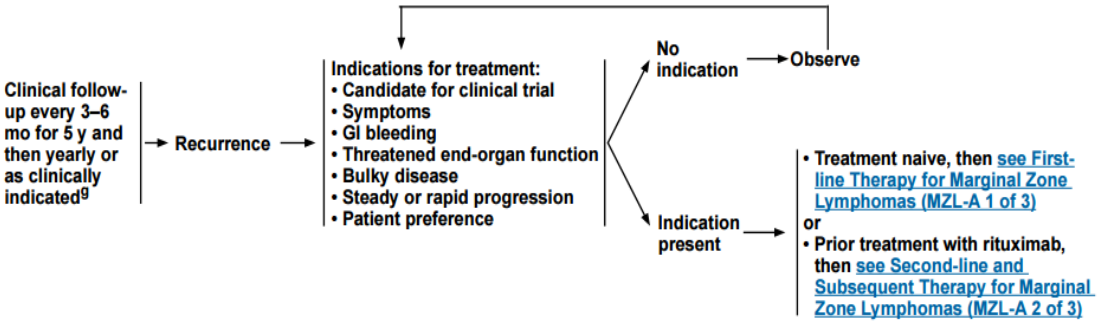
FOLLOW-UP



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SUGGESTED TREATMENT REGIMENS[a,b,c]

First-line Therapy
- **Preferred regimens (in alphabetical order)**
  - **Bendamustine + rituximab**
  - **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)**
  - **RCVP (rituximab, cyclophosphamide, vincristine, prednisone)**
  - **Rituximab (375 mg/m² weekly for 4 doses) (preferred for SMZL)**
- **Other recommended regimens (in alphabetical order)**
  - **Ibritumomab tiuxetan[d,e] (category 2B)**
  - **Lenalidomide + rituximab (category 2B)**

First-line Therapy for Elderly or Infirm (if none of the above is expected to be tolerable in the opinion of treating physician)
- **Rituximab (preferred) (375 mg/m² weekly for 4 doses)**
- **Chlorambucil + rituximab**
- **Cyclophosphamide + rituximab**
- **Chlorambucil**
- **Cyclophosphamide**

First-line Extended Therapy (optional)
- **If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m² one dose every 12 weeks**

See Second-line and Subsequent Therapy on MZL-A 2 of 3

For patients with locally bulky or locally symptomatic disease, consider ISRT 4–24 Gy ± additional systemic therapy.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens MZL-A 3 of 3.
[b]The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.
[c]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by

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SUGGESTED TREATMENT REGIMENS[a,b,c]
(in preference order)

Second-line and Subsequent Therapy
- Bendamustine + rituximab
- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- RCVP (rituximab, cyclophosphamide, vincristine, prednisone)
- Rituximab
- Ibrutinib[f]
- Lenalidomide ± rituximab
- Bendamustine + obinutuzumab
- Idelalisib[f] (refractory to both alkylator and rituximab)
- Ibritumomab tiuxetan[d,e] (category 2B)

Second-line and Subsequent Therapy for Elderly or Infirm (if none of the above is expected to be tolerable in the opinion of treating physician)
- Rituximab (preferred) (375 mg/m^2 weekly for 4 doses)
- Chlorambucil + rituximab
- Cyclophosphamide + rituximab
- Chlorambucil
- Cyclophosphamide

Second-line Consolidation or Extended Dosing (optional)
- If treated with bendamustine + obinutuzumab for recurrent disease then obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 wks for total of 12 doses)
- High-dose therapy with autologous stem cell rescue
- Allogeneic hematopoietic cell transplant for highly selected patients

For patients with locally bulky or locally symptomatic disease, consider ISRT 4–24 Gy ± additional systemic therapy.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens MZL-A 3 of 3.
[b]The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.

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special article

Annals of Oncology 24: 857–877, 2013
doi:10.1093/annonc/mds643
Published online 20 February 2013

ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma

M. Dreyling[1*], C. Thieblemont[2], A. Gallamini[3], L. Arcaini[4], E. Campo[5], O. Hermine[6], J. C. Kluin-Nelemans[7], M. Ladetto[8], S. Le Gouill[9], E. Iannitto[10], S. Pileri[11], J. Rodriguez[12], N. Schmitz[13], A. Wotherspoon[14], P. Zinzani[15] & E. Zucca[16]

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Received 19 September 2012; revised 4 December 2012; accepted 5 December 2012

Discussion

- Criteria for initiating treatment in SMZL are the following:
  - progressive or painful splenomegaly;
  - one of the following symptomatic/progressive cytopenias:
    - Hb <100 g/l
    - platelets <80 x 10^9/l
    - neutrophils <1.0 x 10^9/l
- Therapeutic options:
  - splenectomy
  - chemotherapy: rituximab alone or rituximab-chemotherapy

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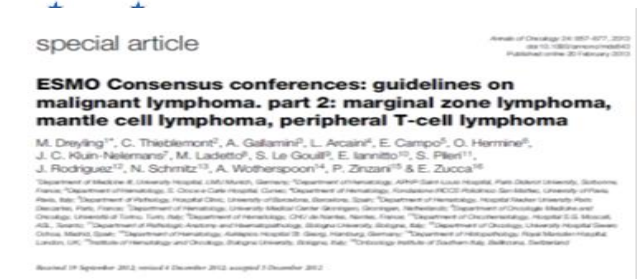
Discussion



special article

ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma

M. Dreyling[1*], C. Thieblemont[2], A. Gallamini[3], L. Arcaini[4], E. Campo[5], O. Hermine[6], J. C. Kluin-Nelemans[7], M. Ladetto[8], S. Le Gouill[9], E. Iannitto[10], S. Pileri[11], J. Rodriguez[12], N. Schmitz[13], A. Wotherspoon[14], P. Zinzani[15] & E. Zucca[16]

RESPONSE CRITERIA

❖ **Complete response:**

– Resolution of organomegaly (spleen length < 13 cm).

– Hb >120 g/l, platelets >100 × 10^9/l and neutrophils >1.5 × 10^9/l.

– No evidence of circulating clonal B cells (light chain-restricted B cells) by flow cytometry.

– No evidence of BM infiltration detected by immunohistochemistry.

– Optional: negative DAT and normal PET scan (if positive at diagnosis).

❖ **Partial response:**

– Regression of ≥50% in all the measurable disease manifestations.

– No new sites of disease.

– Improvement of cytopenias.

– Decrease of infiltration and improvement of haemopoietic reserve at BM biopsy.

❖ **No response**

– <10% improvement on the disease manifestations.

❖ **Progression**

– >50% of measurable signs of the disease from nadir.

❖ **Relapse**

– re-appearance of any measurable sign

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Discussion

Thus, therapeutic options for SMZL comprise:

- Active surveillance
- Splenectomy
- Use of the anti-CD20 monoclonal antibody rituximab alone
- Rituximab added to a variety of cytotoxic agents (chemo-immunotherapy) in various protocols.

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- Active surveillance can be a strategy for relatively asymptomatic patients
- Splenectomy is the oldest therapeutic option, can also be diagnostic and safe (by laparoscopy), with high short- and long-term efficacy
- However, splenectomy is no longer the treatment of choice, since rituximab is associated with a better outcome and significantly less toxicity.

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- Rituximab as monotherapy is effective in SMZL and provides better responses, has less toxicity compared to chemotherapy
- Rituximab has little impact on the quality of life, reduces risk of infections, seems to induce durable remissions and can be used again at relapse
- Clinical and laboratory responses are fast, with improvement in blood counts in about eight weeks

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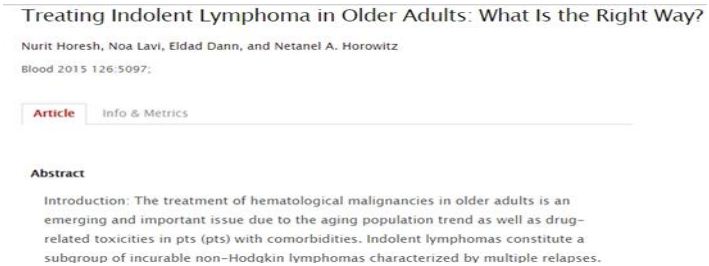

Treating Indolent Lymphoma in Older Adults: What Is the Right Way?

Nurit Horesh, Noa Lavi, Eldad Dann, and Netanel A. Horowitz

Blood 2015 126:5097;

Article | Info & Metrics

Abstract

Introduction: The treatment of hematological malignancies in older adults is an emerging and important issue due to the aging population trend as well as drug-related toxicities in pts (pts) with comorbidities. Indolent lymphomas constitute a subgroup of incurable non-Hodgkin lymphomas characterized by multiple relapses.

Chemo-immunotherapy in various protocols

- Anthracycline containing chemo-immunotherapy regimens (ACR) such as R-CHOP are very active in indolent lymphomas
- Due to their high rate of associated toxicities such regimens are less likely to be given to the elderly population
- The present analysis of a cohort of older adults with indolent lymphoma treated with chemo-immunotherapy regimens in routine clinical practice has demonstrated that ACR was safe and efficacious
- The patient's age should not deter physicians from using ACR in older adults.

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Discussion

What about our patient?

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- While the results of immunohistochemistry of bone marrow were being prepared, our patient was initially started on 1 mg/kg prednisolone
- After 10 days of therapy:

▪ Blood count: Hb 87 g/l, WBC 4.21 x 10^9/l, Platelet count 118 x 10^9/l

▪ Abdominal examination showed persisting splenomegaly about 13 cm below the left costal margin

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Discussion

What about further treatment?

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Discussion

- ✓ Because of AIHA and massive splenomegaly, active surveillance is not appropriate
- ✓ Splenectomy is not recommended due to advanced age and high risk of post-splenectomy complications
- ✓ Rituximab at 375 mg/m^2 × 4 weekly doses is a reasonable first-line therapy and a real and less traumatic alternative to splenectomy.

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Conclusion

Our patient is going to be treated with rituximab monotherapy for both lymphoma and secondary AIHA.

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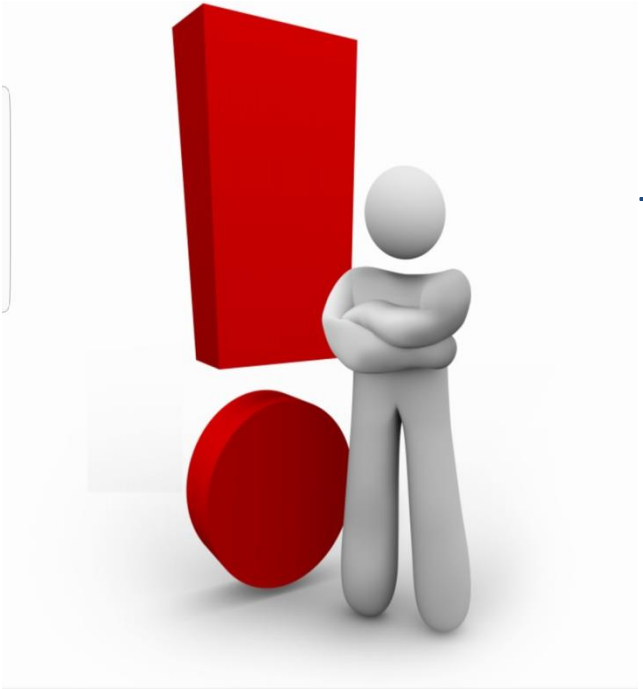

Thank you for your attention!