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Advanced stage Hodgkin Lymphoma: patient management

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Summary. Hodgkin lymphoma (HL) is a rare cancer of the lymphoid system. It clinically presents with swollen lymph nodes and/or systemic symptoms, such as fever, night sweats, or weight loss, as signs of a more advanced stage disease. For the purpose of treatment allocation, HL cases are classified as early-stage favorable, early-stage unfavorable, and advanced-stage disease. Here below we describe four different clinical cases from real life that address some key issues and medical needs that are present in the daily practice with patients affected by advanced stage HL. The four clinical cases are quite heterogeneous, but in each case there are strong inputs to manage a specific category of advanced phase HL patient that is going to be treated with first-line therapy.

Key words: Hodgkin Lymphoma; advanced stage; first-line treatment

Hodgkin lymphoma (HL) is a rare cancer of the lymphoid system. It clinically presents with swollen lymph nodes and/or systemic symptoms, such as fever, night sweats, or weight loss, as signs of a more advanced-stage disease.

HL is one of the most common malignancies in young adults, however it can occur at all ages: recently, an increase of the incidence in people older than 70 years has been reported, while the peak incidence between 20 and 30 years of age appears to be stable. In Europe, 18,525 cases are expected annually (1).

For the purpose of treatment allocation, HL cases are classified as early-stage favorable, early-stage unfavora- ble, and advanced-stage disease (1).

The response rates following a treatment that includes mul-ti-agent chemotherapy in all cases and consolidative radiation therapy (RT) in limited stages of the disease, are high, with long-term remission rates ranging from 80% to 90%, depending on risk group, age, and treatment.

The initial treatment in HL patients with advanced-stage disease is guided by an interim PET scan after 2 cycles of systemic therapy (PET-2), and consists of 6 cycles of multi-agent chemotherapy and localized RT to PET-positive residues thereafter (1).

The combination of doxorubicin, bleomycin, vinblas- tine and dacarbazine (ABVD) has become the widely accepted standard regimen for first-line therapy, as it is associated with a considerably lower acute and long-term toxicity, when compared with the escalated combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) chemotherapy regimen, and is potentially suitable also for elderly patients.

Moreover, the BEACOPP regimen is more often complicated by long-term toxicities, such as sterility

and occurrence of second cancers. However, the risk for refractory disease or re- lapsed HL are significantly higher following the ABVD treatment in comparison to the BEACOPP regimen (1).

The aim of three recently reported large randomized phase III trials, namely the RATHL, HD18 and AHL2011 trials, was to develop individualized approaches, based on an initial therapy with either escalated ABVD or BEACOPP regimens, guided by interim PET scans (1).

The French AHL2011 trial recently reported a non- inferior four-year Progression-Free Survival (PFS) of 87.1% with randomized deescalation to 4x ABVD in patients who achieved a PET-2–negative status after 2x BEACOPP escalated *vs.* 87.4% with full 6x BEACOPP escalated (1).

High-dose chemotherapy (HDCT), followed by autologous stem cell transplantation (ASCT), is administered to patients with primary refractory and relapsed disease, if feasible, and can result in long-term remission in up to 50% of cases (1). Risk factors for relapse after HDCT have been described, as progression/early relapse, involvement of extranodal disease, and residual PET-positive disease before HDCT.

More recently, several targeted agents were investigated in this setting, such as the antibody-drug conjugate brentuximab vedotin (BV) and the checkpoint inhibitors nivolumab and pembrolizumab. The two checkpoint inhibitors nivolumab and pembrolizumab target PD-1 on exhausted T-cells and other immune cells and were approved for the treatment of patients with relapsed/refractory Hodgkin Lymphoma (rrHL). Nivolumab and pembrolizumab showed overall response rates (ORRs) of 69% and 65%, respectively, and a complete response rate (CRR) of 16% with long lasting responses in patients achieving a partial remission (PR) in pivotal phase II trials (1).

Experiences from the clinical practice often allow a better understanding of the patients' needs and can possibly help the tailoring of patient-specific therapeutic strategies.

Here below we describe four different clinical cases from real life that address some key issues and medical needs occurring in the daily practice with patients affected by advanced-stage HL.

Clinical case 1

In March 2018, a young man aged 24 without any significant clinical history, referred to the haematological center because of weight loss, fever and night sweats, with appearance of mediastinal region expansion. A biopsy diagnosed a classical Nodular Sclerosis Hodgkin lymphoma (NSHL). Blood tests and serology were in the normal range. CT/PET scan performed at diagnosis showed:

- A 12 cm mediastinal mass intensely hypermetabolic (standardized uptake value [SUV] max 17), with infiltration of the contiguous pulmonary parenchyma of the upper lobe;
- Multiple intensely hypermetabolic lymphadenomegalies (SUV not available) in laterocervical and bilateral retroclavicular regions, in the axillary cavity deep behind the pectoral muscles and in almost all the mediastinal stations, at the pulmonary hylum, along the mammary chain and in the posterior mediastinum;
- Increased concentration of the radiopharmaceutical agent in the skeletal medulla of almost all the body districts in the field of vision (SUV not available);
- Slight increase of the tracer concentration in the spleen (SUV not available);

The patient was staged IV B International Prognostic Score (IPS) according to the Hasenclever score (2).

The first-line therapy was started and 6 cycles of the ABVD regimen were scheduled.

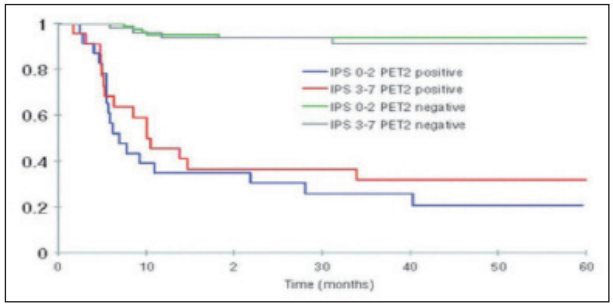
After the second cycle, an Interim PET scan was performed:

- Persistence of hyperfolding area (SUV max 9) in the left anterior mediastinal area, with involvement of the contiguous pulmonary parenchyma of size and uptake with respect to the onset;
- Persistence of bone marrow uptake (with possible influence of the G-CSF use) in all the segments reported, even if reduced (SUV not available);
- Modest and circumscribed fixation area (SUV max 2.8) in the left pulmonary basal area.

Lack of standardized response assessment criteria

- Dimensional mass reduction.

At this stage the answer was doubtful; consequently, the correlation between IPS and PET-2 was evaluated:



Following the interim PET scan, the patient was considered in partial response and continued the first-line therapy with the remaining 4 cycles of the ABVD regimen.

In October 2018, the 6 cycles of ABVD were completed and a restaging was done. The PET scan showed:

- Appearance of the hyperfunctioning area of the radiopharmaceutical agent in the left paratracheal site (SUV max 11), before the trachea in the right paramedian area (SUV max 3.3), left retropectoral (SUV max 93), right paratracheal (SUV max 5.9), anteromedially to the thoracic aorta (SUV max 9.4) and in the left pulmonary ilo-paraxial region (SUV max 10);
- Appearance of the hyperfunctioning area of the radiopharmaceutical agent (most likely lymph nodes) in place: left paratracheal (SUV max 11) unchanged the hyperfolding area in the left anterior mediastinal region (SUV max 9), with involvement of the contiguous pulmonary parenchyma.

The CT scan showed the reduction of the expansive process involving the anterior mediastinal space and extending caudally to incorporate the large vessels.

A disease progression was evaluated, and consequently the patient started a second-line therapy with the ifosfamide, gemcitabine, vinorelbine and prednisone (IGEV) regimen, followed by ASCT. The PET scan after the second cycle of IGEV treatment revealed:

- Permanence, but reduced intensity, of accumulations in the left paratracheal site (SUV max 6), ipsilateral retropectoral (SUV max 3.3) and in the left pulmonary hilum-paraxial region (SUV max 3.7);
- The hyperfolding area was substantially unchanged (SUV max 9), perhaps slightly less extensive in the left anterior mediastinum, with involvement of the contiguous pulmonary parenchyma;
- An area of modest uptake at the left pulmonary base was still present as well.

Considering these results, the disease was evaluated persistent and therefore the patient started a therapy with BV as a bridge to transplantation. The treatment is still ongoing.

Case 1 discussion

There are some considerations for this case:

- The persistence of bone marrow uptake could be influenced by the use of G-CSF.
- The interim PET scan was evaluated as partial response but there is no indication about the criteria used for the evaluation.
- The patient was evaluated as affected by progressive disease; nevertheless, he was not submitted to biopsy of the significant lymphoadenopathy to histologically confirm the persistence of HL.
- We should consider that the response to pre-transplantation salvage chemotherapy remains the most important prognostic factor for the outcome in HL patients. The decision to use IGEV instead of the bendamustine, gemcitabine, and vinorelbine (BEGEV) regimen as a bridgeto transplantation found a rational in strong previous experience: Santoro *et al.* reported the encouraging results derived from the induction regimen obtained in 91 patients with refractory or relapsed HL that were treated prospectively with ifosfamide 2000 mg/m^2 on days 1 to 4, gemcitabine 800 mg/m^2 on days 1 and 4, vinorelbine 20 mg/m^2 on day 1, and prednisolone 100 mg on days 1 to 4 (IGEV).

The 53.8% of patients achieved a CR and the 27.5% a partial response for an ORR of 81.3%. Adequate CD34+ cell collection was achieved in 98.7% of mobilized patients. The regimen appeared to be well tolerated and manageable from the patients.

The high response rate and the low toxicity profile, and the very high mobilizing potential of the IGEV regimen strongly confirmed that patients with relapsed/refractory HL may benefit from the use of this salvage induction regimen (2).

Clinical case 2

In April 2012, a 27 year-old female was referred to the haematological center for an enlargement of the supraclavicular lymph nodes and night sweats.

A biopsy was performed and a diagnosis of classical NSHL was done.

After bone marrow biopsy, PET and CT scans, a stage IV x B was deter- mined according to the Ann Arbor staging system based on the presence of disease in left supraclavicular nodes, mediastinum, liver (PET positive for nodular lesions in segment III) and lung (bulky disease in the upper left lobe 8 x 4.8 x 9 cm; SUV max 20.41). A diffuse and homogeneous marrow uptake was not considered as disease involvement.

The IPS score was 3, consistently with stage, leucocytosis, lymphocytopenia.

The patient was enrolled in the HD0801 protocol and started the treatment with the ABVD regimen.

In the protocol, PET-2-positive patients were able to shift to an intensified treatment with IGEV followed by ASCT, while PET-2-negative patients completed 6 cycles of the ABVD regimen.

As per protocol, the patient underwent a PET scan after 2 ABVD cycles. The interim PET scan showed:

- The disappearance of all lesions detected at the baseline PET scan;
- A focal uptake in the maxillary bone, considered secondary to an odontogenic infection.

The patient completed the 6 cycles of the ABVD regimen and a restaging with CT and PET scans was performed. The CT scan showed:

-A residual lesion measuring 2 cm in the major axis in the upper lobe of the left lung;

- The resolution to less than 1.5 cm of the nodal lesions. Consequently, considering the absence of pathological uptakes at the end of the treatment, a CR was evaluated.

According to the HD0801 protocol, the patients in CR were randomized to consolidative RT of the bulky lesions at baseline or to observation. The patient was randomized to observation only but, after a preliminary internal discussion and the subsequent discussion with the patient, it has been decided to start the RT considering the site (the lung), and the dimension of the baseline bulky lesions.

So, the patient withdrew from the protocol and received 30.6 Gy in 17 fractions of 1.8 Gy each.

After 70 months, the patient is still in CR without any treatment toxicity.

Case 2 discussion

There are some considerations for this case:

Indeed, the protocol regimen that was applied for this patient was a real effective approach.

The phase II HD0801 study involved 519 patients with advanced-stage *de novo* HL submitted to an initial treatment with the ABVD regimen and an early ifosfamide-containing salvage treatment, followed by stem cell transplantation if they showed a positive PET scan evaluation after 2 cycles of chemotherapy (PET-2).

The primary endpoint was the 2-year PFS calculated for both PET-2-negative patients (who completed a full treatment of 6 cycles of the ABVD regimen) and PET-2-positive patients.

Overall, 103 out of the 512 evaluable patients were PET-2-positive. On intention-to-treat analysis, the 2-year PFS was 76% for the PET-2-positive patients (regardless of the salvage treatment they received) and 81% for the PET-2-negative patients (3).

Clinical case 3

In February 2015, a 67-year-old male was referred to the haematology outpatient clinic because of a swelling of the right axilla associated with B-symptoms, consisting in periodic fever higher than 38°C, and drenching night sweats. On clinical examination, the patient had a palpable lymph node of 5 x 3 cm in the right axilla.

Lymph node biopsy was performed and histological ex- amination showed CD30+ Reed-Sternberg cells with weak PAX5 and sporadic CD15 expression, organized in microgranulomas and surrounded by a rich infiltration of CD3+ lymphocytes and macrophages. Diagnostic conclusion was HL.

The CT scan revealed enlarged axillary lymph nodes, and thoracic and abdominal lymph nodes of about 1 cm.

The staging PET-CT scan revealed:

- ^{18}Fluorodeoxyglucose (^{18}FDG)-avid disease in the right retroclavicular, axillary and retropectoral area, in the anterior mediastinum, the paratracheal, right hilar, right cardiophrenic angle, in the upper abdomen (celiac, interportocaval, left paraortic) and right iliac area.

– The spleen showed diffuse and irregular uptake. Bone marrow biopsy was negative for lymphoma infiltration.

Stage was defined as IIIsB, while the IPS was 2 because of age >45 years and of male sex.

The medical history was positive for surgery of aneurysm of the ascending aorta, with replacement by a tubular prosthesis in 2013. The patient was a former smoker.

He was in medical treatment for hypertension with the beta-blocker agent bisoprolol 2.5 mg, 1 tablet/die, and the angiotensin II receptor antagonist telmisartan 80 mg, 1 tablet/die, and received prophylaxis with acetylsalicylic acid 100 mg/die.

Echocardiography documented a slight enlargement of the left atrium and ventricle, with preserved ejection fraction (65%).

The N-terminal pro-hormone natriuretic peptide (NT- proBNP) level was slightly high (296 pg/mL, *vs.* the upper normal value of 150 pg/mL).

Pulmonary function tests, including diffusing capacity of the lung for carbon monoxide (DLCO) and arterial blood gas analysis, resulted in the normal range.

In March 2015, the patient started a treatment with the first of 6 cycles of the ABVD regimen at standard dose. Supportive therapy included the administration of the myeloid growth factor G-CSF on days 8 and 9 following each administration of chemotherapy. Therapy was administered as scheduled.

The interim PET-CT scan documented a complete metabolic response with a minimal uptake in supradiaphragmatic lymph nodes, above the mediastinal blood flow but lower than liver (score 2 according to the 5-point Deauville scoring system), and absence of FDG uptake in the abdominal lymph nodes.

The patient continued the therapy as scheduled.

Monitoring of NT-proBNP showed slightly high, but stable levels (336 pg/mL), while the troponin test was negative.

In July 2015, after the fourth cycle of the ABVD regimen, the patient reported shortness of breath during physical activity. Auscultation of the lung was normal, chest X ray did not reveal any abnormality. The pulmonary function test showed normal DLCO, but a significant reduction of arterial pO_2 (from 100 mmHg to 71 mmHg).

Bleomycin was omitted from the last 2 cycles of chemotherapy, and the patient completed the 6 cycles. Respiratory symptoms resolved, and pulmonary function tests at end of therapy documented an increase of arterial pO_2, and DLCO in the normal range.

The PET-CT scan at end of therapy was unchanged with respect to interim PET scan (Deauville score 2).

Four years after the diagnosis, the patient continues to be in CR and in a good health status.

Case 3 discussion

There are some considerations for this case:

-PET-CT scan resulted in an upstaging of disease with respect to CT scan, detecting also FDG-avid disease in abdominal pericentrimetric lymph nodes and spleen.

– The change from stage IIB without bulk to stage IIIsB resulted in a change of the treatment strategy from a potential combined treatment modality with an abbreviated chemotherapy to a full course of 6 cycles of the ABVD regimen.

– The patient had cardiac and limited pulmonary comorbidity, as he was a former smoker, but the patient did not experience cardiotoxicity despite the full dose doxorubicin. Doxorubicin replacement with the liposomal formulation (Myocet), while maintaining the ABVD regimen as backbone, did not result in a better tolerability of the regimen in an Italian multicenter study for elderly HL patients.

– The patient developed respiratory symptoms after the fourth cycle of the ABVD regimen. Bleomycin is associated with an increased risk of pulmonary toxicity in elderly patients, most often observed after the third or fourth cycle. Although the patient did not show the typical clinical and radiological signs of bleomycin-induced pneumonitis, the decrease in arterial pO_2 could have been an early sign of lung damage. This patient did not require therapy with corticosteroids, and the omission of bleomycin was sufficient to normalize the lung function.

– The RATHL study recently demonstrated that bleomycin can be safely omitted following a negative interim PET scan in patients with advanced HL, with excellent results for disease control. Omission of bleomycin after the negative PET scan result fol-

lowing the second cycle in our patient could have been a safe strategy to avoid initial lung injury. Another potential strategy to avoid pulmonary toxicity in advanced-stage patients at risk is bleomycin replacement with BV.
- The A-AVD regimen is associated with a reduced pulmonary toxicity and an increased efficacy.

In conclusion, the treatment of elderly HL patients remains challenging, as efficacy optimization and reduction of the risk of toxicity should be combined.

Clinical case 4

In March 2015, a 42-year-old woman was referred to the haematological center for a large mediastinal mass (21 x 15 cm) with dyspnea, dry cough and shortness of breath on minimal exertion.

On presentation, the patient was febrile (38.5°C), referring night sweats, and weight loss; blood pressure was 117/81 mm Hg and pulse was regular (140 bpm). The respiratory rate was 28/min, with oxygen saturation of 93% on room air. Heart sounds were diminished, while lung auscultation showed a reduced right side air entry. Other outcomes of the physical examination were in the normal range.

CT-scan and ^{18}FDG-PET scan revealed active disease in the chest due to:
- A large anterior mediastinal mass encasing the great vessels, including the right upper pulmonary artery and the superior vena cava;
- There was at least 50% tracheal compression by mass;
- The right lung was collapsed, with massive pleural effusion and pericardial effusion;
- Laterocervical and supraclavicular right lymph nodes (30 x 40 mm), paraesophageal, para-aortic, mesenterium lymph nodes and liver were also involved.

Excisional biopsy of supraclavicular right lymph node revealed cHL, nodular sclerosis subtype, not Epstein-Barr virus (EBV)-associated in advanced-stage, unfavorable disease (stage IVB and IPS of 4 based on stage, hemoglobin level of 9.8 mg/dL, absolute white cells count 16500 cells/mm^3, absolute lymphocyte count 450 cells/mm^3).

The patient started a treatment with the ABVD regimen.

^{18}FDG-PET scan after 2 cycles was positive and, based on the promising results of PET-2-adapted therapy, the switch to a most efficacious regimen, such as stem cell collection and ASCT, was proposed.

However, due to her religious beliefs, the patient re- fused any high-dose regimen that could expose her to both autologous and heterologous blood component. For this reason, she accepted the salvage treatment followed by early evaluation, according to standard BEACOPP regimen.

Since after 4 BEACOPP courses the patient achieved only a partial remission, and the ^{18}FDG-PET scan was still positive, the patient accepted an early further salvage treatment with the IGEV regimen, and with 40,000 UI EPO twice a week in place of blood transfusions.

After 2 IGEV courses, the patient achieved only a par- tial remission, and the ^{18}FDG-PET scan was still positive, so she was referred to further salvage treatment with 1.8 mg/kg BV administered every 3 weeks by IV infusion, in a named national program.

After 4 cycles, the CT-PET scan showed a reduction in size and intensity of the ^{18}FDG uptake, so the scheduled treatment was completed with additional 12 BV cycles, obtaining the PET-scan negativity after 8 cycles.

The CT scan confirmed a not-active mediastinal mass with a progressive size reduction during the treatment (7.5 x 5 cm after 8 cycles, 6 x 4 cm after 12 cycles, 5 x 3 cm after 16 cycles), and an excellent performance status.

The patient completed the treatment in August 2017, and she is still in follow-up.

Case 4 discussion

This clinical case can suggest some considerations:

The potential benefits of a PET/TC scan-adapted therapy are:

1) Negative interim PET scan: reduce the treatment intensity in rapid response after 2 cycles of chemotherapy, perceived to be at low risk of treatment failure; 2) Positive interim PET scan: intensify the treatment in patients for whom the initial treatment has been less effective (20%) (1). Retrospective studies of patients treated with the ABVD regimen suggested that the FDG-PET scan performed after 2 cycles of treatment

can be highly predictive of treatment success or failure (4). This appears to provide better prognostic information than CT scans, (5) with a high negative predictive value, giving a 2-year PFS of approximately 95% and a reasonable positive predictive value, with PFS between 13% and 27% (6,7).

- The international Response Adjusted Therapy for Hodgkin Lymphoma (RATHL) study (4) tested the use of FDG-PET scans after 2 initial cycles of the ABVD regimen in more than 1200 patients, after which those with an interim PET scan score ranging from 1 to 3 were randomly assigned to either continuation of the ABVD treatment or to receive doxorubicin, vinblastine, and dacarbazine (AVD) without bleomycin to determine whether the pulmonary toxicity could be reduced for patients with a good prognosis. Conversely, patients with an interim PET scan score from 4 to 5 proceeded to intensification with the BEACOPP regimen every 3 weeks or with the similar BEACOPP-14, administered at 2-week intervals.
- The Italian lymphoma group study (9) used a similar approach, with interim FDG-PET scans after 2 cycles of the ABVD regimen followed by intensification to the BEACOPP regimen for patients with positive scans. The rates of metabolic remission after 2 cycles of theABVD regimen were very similar in all the 3 trials, at about 85%. The results of treatment in the PET-positive group were also similar and appeared to be superior to the historical controls used in previous studies, with subsequent metabolic response rates of 75% or more and projected failure-free survival figures at 2 years of 65- 75%.

The antibody-drug conjugate BV combines an antibody to the CD30 molecule, which is expressed on Reed-Sternberg cells, with an antitubulin, monomethyl auristatin E. The efficacy seen in early-phase studies has been impressive, with 76 objective responses (and 34% CRs) among 102 patients with recurrent disease who had already undergone high-dose therapy and autologous stem cell rescue (10-11-12).

- Pembrolizumab and nivolumab are two anti-PD-1 antibodies that have undergone phase 1 trials, with re- ported response rates of 53% and 87%, respectively (13). Nivolumab is currently being assessed in a phase 2 trial in patients whose disease has progressed after ASCT (14).
- A range of salvage therapies has been tested in the 20-30% of patients with advanced disease whose HL was refractory to, or relapsed after initial treatment. The salvage regimens appear to be largely interchangeable. The single-arm phase 2 trials performed did not offer a direct comparison between regimens, but ORR of 60% to 80% have been found (15). A randomized comparison of sequential single-agent high-dose therapy *vs.* continued conventional salvage therapy did not show any difference in efficacy (16).

Favored salvage regimens in our center include ifosfamide, carboplatin and etoposide (ICE), epirubicin in place of carboplatin (IVE), and cytarabine and cisplatin (DHAP).

- Patients who are eligible and achieve a complete metabolic response should proceed ASCT in second remission (17).
- Assuming a successful mobilization of stem cells, the standard high-dose regimen used prior to stem cell transplantation is carmustine, etoposide, cytarabine, and melphalan (BEAM). This regimen is based on 2 randomized controlled trials that compared high-dose chemotherapy followed by ASCT to conventional chemotherapy in patients achieving a second remission. Both studies showed a significantly improved freedom from progression in the group receiving high-dose therapy, although the small number of patients enrolled prevented the conclusive demonstration of improved OS (18,19).

Conclusion

The four clinical cases we reported are quite heterogeneous but in each case there are strong inputs to manage a specific category of advanced-phase HL patient that is going to be treated with first-line therapy.

Indeed, we discussed both young and elderly patients' cases. Patients with an early relapse and the role of PET scans in treatments and in disease evaluation were discussed as well.

It is important to remind that new drugs and clinical trials are allowing to treat in advance the patients with a sort of tailored therapy that could bring to a long disease remission and a good quality of life. An early

identification of the most appropriate regimen for the patient is crucial for the treatment outcome.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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