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MYELODYSPLASTIC SYNDROMES (M SAVONA, SECTION EDITOR)

Treatment of MDS/MPN and the MDS/MPN IWG International Trial: ABNL MARRO

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Abstract

Purpose of Review MDS/MPNs comprise a group of rare hematologic malignancies that balance features of myeloproliferation and bone marrow failure. Given overlapping clinical features and rarity of incidence, MDS/MPNs have long posed a diagnostic and therapeutic challenge. Herein, we sought to review recent advances in diagnosis and emerging therapeutic strategies and highlight the upcoming ABNL MARRO study which aims to individualize therapy for patients with MDS/MPN.

Recent Findings Focused study of molecular mutations in MDS/MPNs has provided improved diagnostic clarity. Specific gene mutation or patterns of mutation have been increasingly described and have helped to distinguish between clinically similar diseases. While the current treatment landscape consists largely of therapies that have been co-opted from related disease, the emergence of prospective clinical trials specifically focused on MDS/MPN and the increased use of targeted agents represent progress for patients with MDS/MPN.

Summary An improved understanding of the molecular drivers of myeloid diseases has provided diagnostic clarity and renewed hope of targeted therapies for MDS/MPN patients. The upcoming ABNL MARRO study hopes to leverage this knowledge to match patients with targeted therapeutic options specific to molecular drivers of their disease.

Keywords Myeloid neoplasms · Myelodysplasia · Myeloproliferative · Overlap syndromes

Introduction

The 2016 World Health Organization (WHO)-defined category of myelodysplastic/myeloproliferative neoplasms (MDS/MPN) embodies the challenges inherent in assigning categorical definitions to diseases that exist along a spectrum [1]. Formerly referred to as myelodysplastic/myeloproliferative diseases (MDS/MPD), this category was formally established in the 2002 WHO classification of myeloid neoplasms, at which time the category was comprised of chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), and myelodysplastic/myeloproliferative disease, unclassifiable (MDS/MPN-U). The formation of the MDS/MPD category acknowledged that myeloid diseases frequently present with both proliferative and dysplastic features. Prior to this, diseases with overlapping features were arbitrarily assigned to either MDS or MPN categories [2–4]. In successive iterations of WHO classification systems, the category has remained largely intact, with the subtle renaming of aCML to aCML, *BCR-ABL1*$^-$ to more clearly distinguish it from the Philadelphia chromosome-containing chronic myeloid leukemia, *BCR-ABL1*$^+$. Additionally, MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T, previously known as refractory anemia with ring sideroblasts and thrombocytosis [RARS-T]) was upgraded from a provisional to full entity within this category [1, 5].

A growing knowledge of molecular abnormalities has contributed to improved diagnostic characterization of MDS/MPN given our understanding that mutations involving certain genes or gene combinations are enriched in specific disease states (i.e., *SETBP1* and *ETNK1* in aCML, *TET2/SRSF2* in CMML, RAS/MAPK pathway mutations in JMML, and

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SF3B1 in combination with *JAK2/MPL/CALR* in MDS/MPN-RS-T) [1]. Nevertheless, extensive genomic and transcriptomic profiling of this group of diseases suggests they should be viewed as a continuum rather than distinct entities [6••]. Unfortunately, improved molecular understanding has been slow to translate into improved therapeutic options, as most patients are treated with the same agents that would have been used two decades ago. The data supporting these therapeutic strategies is often extrapolated from studies of MDS or MPN patients, reflecting the paucity of prospective, later phase, interventional trials focusing specifically on MDS/MPN patients. The few prospective studies that have been published have been early phase and function more as proof concept rather than illustrating a therapeutic path forward [7–10]. Herein, we will review the spectrum of MDS/MPNs, highlight current treatment strategies, discuss emerging therapeutic strategies, and review the proposed ABNL MARRO study that aims to leverage our molecular knowledge of these diseases into targeted therapeutic approaches on an international scale.

Diagnostic Criteria and Dilemmas

The 2016 revision to the WHO classification of myeloid neoplasms includes CMML, aCML, JMML, MDS-MPN-RS-T, and MDS/MPN-U within the MDS/MPN category. Although unified by overlapping features of ineffective hematopoiesis and myeloproliferation, these disease entities are relatively distinct, with characteristic laboratory and/or morphologic features and, often, a common molecular correlate. CMML displays a persistent absolute and relative monocytosis with recurrent mutations involving one or more of *TET2*, *SRSF2*, and *ASXL1* in addition to RAS pathway mutations in "proliferative-type" CMML subtypes. Atypical CML is characterized by a leukocytosis comprised of frequent immature myeloid forms and dysgranulopoiesis along with mutations involving *SETBP1* and/or *ETNK1*. MDS-MPN-RS-T displays the eponymous ring sideroblasts and thrombocytosis, defined by a platelet count of over 450,000 cells/dL, along with frequent *SF3B1* and MPN driver mutations in *JAK2*, *MPL*, or *CALR*.

Despite and, on occasion, due to the incorporation of mutation data into the diagnostic approach to MDS/MPNs, several recurrent diagnostic challenges continue to arise. While not comprehensive, we will highlight three challenges often seen in our clinical practice. First, we will discuss a patient that presents with coexisting monocytosis and bone marrow fibrosis. Second, we will address the challenge of distinguishing between aCML and chronic neutrophilic leukemia (CNL), and, last, we will highlight the challenge in diagnosing MDS/MPN-RS-T.

Multiple studies have indicated that monocytosis is present in nearly 20% of primary myelofibrosis (PMF) patients at presentation, is a poor prognostic feature, and represents an accelerated form of the disease [11–13]. Monocytosis is present in a similar proportion of polycythemia vera (PV) patients and may negatively impact survival in this disease as well [14]. Alternatively, MPN driver mutations, most commonly a *JAK2 V617F* mutation, are seen in approximately 10% of patients with CMML. While this appears to have some impact on clinical phenotype, it does not impact survival outcomes [15]. Interestingly, in JAK2 mutant CMML, myelofibrosis with monocytosis, and PV with monocytosis, mutations involving *TET2*, *SRSF2*, and *ASXL1* occur with increased frequency, implying a loose genotype-phenotype correlation [11, 14, 15]. Recent work has also suggested the morphologic diagnosis of CMML and PMF in this group with overlapping features may correlate with the *JAK2* V617F allelic burden [16]. Discerning between these entities can be accomplished in several ways. A detailed history can often reveal the initial presence of an MPN prior to the later development of monocytosis which, by WHO definition, would negate a CMML diagnosis in favor of MPN with monocytosis. Additionally, close pathologic review may reveal either hypersegmented megakaryocytes with associated clustering typical of a MPN or absence of typical megakaryocyte morphology that would favor a CMML diagnosis. Flow cytometry of monocytes can also be utilized to identify an increase in classical monocytes which has been shown to be specific to CMML [17]. Alas, this may be a clinically moot point, as *JAK2* mutant CMML and PMF with monocytosis tend to share similar mutational profiles and have similarly poor prognoses, suggesting a rose—or more appropriately, a thorn—by any other name, would hurt just as much.

Distinguishing between aCML and CNL has long been a challenge, although recurring gene mutations have recently provided improved clarity. In reviewing the WHO diagnostic criteria for each, it is evident how differentiation can be difficult. Both present with a neutrophilic leukocytosis accompanied by a hypercellular marrow; however, aCML requires a significant proportion ($\geq 10\%$) of myeloid precursors and evidence of granulocytic dysplasia while CNL features a leukocytosis comprised of mature neutrophils ($\geq 80\%$) with marrow morphology favoring granulocytic hyperplasia over dysplasia. Molecularly, the presence of an activating *CSF3R* mutation favors a CNL diagnosis, while mutations involving *SETBP1* or *ETNK1* more commonly occur in aCML [1]. Unfortunately, *CSF3R* and *SETBP1* mutations are not mutually exclusive and have been reported to coexist in approximately 20% of patients with aCML and CNL [18], suggesting that either our understanding of the molecular drivers of these diseases is limited in its applicability, or our diagnostic criteria create artificial fences by which the diseases are not bound. To that end, it is worth noting that mutations in genes such as *U2AF1*, *ASXL1*, and *TET2* are common in aCML, CNL, and across the myeloid spectrum, not to mention their presence in clonal hematopoiesis.

The third diagnostic dilemma that we will consider is that of the diagnosis of MDS/MPN-RS-T. Patients presenting with

thrombocytosis and anemia face a broad differential diagnosis. Iron deficiency is the most frequent culprit and is hallmarked by the presence of significant microcytosis which triggers the ordering of diagnostic iron studies. Beyond this, inflammatory conditions are responsible for the majority of remaining cases, leaving few remaining cases in which diagnostic definition is required. While a bone marrow biopsy is not diagnostically mandated for cases of ET, this should be pursued in cases with concomitant anemia. If detection of an MPN driver mutation from the peripheral blood precedes a bone marrow biopsy and aspirate, the pretest probability heavily favors PMF or post-ET myelofibrosis. In MDS/MPN-RS-T however, morphologic assessment typically reveals erythroid lineage dysplasia and a significant proportion ($\geq 15\%$) of ring sideroblasts along with the frequent presence of an *SF3B1* mutation. The dual genotype-phenotype correlation reinforces the hybrid nature of this disease [1], and the distinction of MDS/MPN-RS-T from a true MPN carries prognostic and potentially therapeutic significance [19, 20].

Risk-Adapted Therapy

MDS/MPNs are generally considered to be aggressive myeloid diseases that balance myeloproliferation with bone marrow failure. Challenges arise from a molecular complexity that conveys a treatment-resistant phenotype along with an increased propensity to transform into acute myeloid leukemia (AML). MDS/MPN-U, aCML, and CMML have been associated with median survivals of 1–3 years [15, 21, 22]. MDS/MPN-RS-T has more variable outcomes, with survival estimated to range from approximately 1 year in high-risk disease to 8–9 years in lower-risk disease [23, 24]. Risk stratification must take into account the damaging prognostic impact of abnormal cytogenetics and the presence of *ASXL1* or *SETBP1* mutations. [23] Outside of the minority of patients with indolent disease as defined by MDS-/MPN-specific prognostic scores, [25–28] consideration of allogeneic hematopoietic cell transplant (AHCT) is recommended for fit patients. The impact of AHCT in MDS/MPNs has not been robustly studied primarily due to the rarity of disease incidence. Additionally, the studies that have been performed often lump multiple diseases together and fail to reflect the interval advances in diagnostic characterization and transplant technology. A 2004 study by Mittal et al. assessed a group of patients with PMF, CMML, or aCML who underwent AHCT showing a 2-year overall survival (OS) and disease-free survival (DFS) of 47% and 37%, respectively [29]. A contemporaneous study from Germany reviewed eight patients with aCML who underwent AHCT, reporting that all patients engrafted and all but one remained alive at a median follow-up of 55 months post-transplant [30]. A follow-up of this study commented on 21 aCML who had undergone AHCT, noting that 17 of 21 remained alive at five years with median OS after transplant of 46.8 months [31]. A single-center review from South Korea of 10 patients with MDS/MPN (7 CMML, 2 aCML, 1 MDS/MPN-U) reported 5-year OS and relapse-free survival (RFS) of 42% and 52%, respectively. A myeloablative conditioning (MAC) regimen was associated with improved RFS [32]. The largest study to date of transplanted aCML patients assessed 42 patients transplanted between 1997 and 2006 who were reported to the European Society for Blood and Marrow Transplantation (EBMT) registry. Despite variable conditioning regimens, 5-year OS, RFS, and non-relapse mortality (NRM) were 51%, 36%, and 24%, respectively, with relapse occurring in 40% of patients. In this study, 69% of patients were transplanted in the initial chronic phase of the disease while 22% were transplanted in accelerated or blast phase. While this did not reach significance ($p = 0.08$), the 5-year OS for patients in the first chronic phase was 57% compared with 38% in any other phase (i.e., second chronic phase, accelerated phase, blast phase). MAC conditioning regimens were used in 76% of patients [33]. A recent publication of the Mayo Clinic experience in transplanting MDS/MPN patients retrospectively assessed 49 patients (35 CMML, 8 MDS/MPN-U, 5 JMML, 1 aCML, and 0 MDS/MPN-RS-T) who underwent AHCT. Only patients with CMML and MDS/MPN-U were included in the analysis. Eighteen CMML patients without blast transformation prior to transplant were followed for a median of 21 months post-transplant and demonstrated a 21-month OS and NRM rate of 55% and 25%, respectively. Relapse was seen in 29% of patients. Seventeen CMML patients experienced blast transformation prior to transplant and demonstrated 21-month OS and NRM of 47% and 34%, respectively, with a 40% relapse rate. In the MDS/MPN-U cohort, 8 patients underwent AHCT with a 2-year OS of 41%. Relapse was seen in 3 patients at a median follow-up of 15 months [34]. Overall, AHCT appears to have the potential for durable responses in this group of diseases with an otherwise dismal prognosis; however, this comes with high rates of NRM and relapse. Optimization of pre-transplant therapy, conditioning regimens, and targeted maintenance therapy strategies may help to improve these outcomes.

Symptom-Directed Therapy

Aside from AHCT, optimal therapy for MDS/MPNs has not been clearly defined. Historically, interventions have been individualized based on specific symptoms and based on evidence that has largely been extrapolated from larger studies in either MDS or MPN. The dearth of clinical trials that focus specifically on MDS/MPN population is reflected in Table 1. In select cases that lack progressive leukocytosis, anemia, thrombocytopenia, or disease-related symptoms, an approach of active surveillance can be adopted. More recently, an

increased understanding of molecular drivers has allowed for targeted approaches to be considered in a minority of patients.

Proliferative features of MDS/MPNs are often managed with the cytoreductive agent, hydroxyurea, while hypomethylating agents (HMA) and the JAK1/2 inhibitor, ruxolitinib, have become increasingly employed. Hydroxyurea has been shown to produce complete and partial remissions, although these are often short-lived [35–38]. Hydroxyurea is typically used in the setting of progressive leukocytosis or symptomatic splenomegaly and may be utilized as a single agent or in combination [39, 40]. HMAs such as azacitidine and decitabine have become increasingly utilized across the spectrum of MDS/MPNs in an effort to modify the underlying disease, provide cytoreduction, improve cytopenias, or prepare patients for AHCT [7, 21, 41, 42]. While MDS/MPN patients were included in several large trials testing HMAs, these trials were predominantly comprised of MDS patients [7, 43]. In a recent phase 2 study of higher-risk CMML patients, decitabine was associated with an ORR of 48% with a complete response (CR) rate of 17% [44]. These results are consistent with a previously published phase 2 study of decitabine in 39 CMML patients which showed an ORR of 38% and 10% CR rate [45]. A single-center retrospective review of 10 MDS/MPN-U patients treated with either decitabine or azacitidine demonstrated 2 (20%) CRs and 1 (10%) PR with progressive disease seen in 3 (30%) patients [41]. In another single-center review of 85 MDS/MPN-U patients, HMA therapy was the most frequently utilized treatment strategy (42%); however, it was not shown to have a significant impact on OS (16.4 vs 11.5 months, $p = 0.57$) [21]. When used prior to AHCT, HMA therapy has been associated with improved post-transplant outcomes compared with cytotoxic chemotherapy [42]. Venetoclax is a BH3 mimetic that inhibits bcl-2 and has demonstrated impressive response rates in elderly patients with AML when used in combination with either HMAs or low-dose cytarabine [46, 47]. Ongoing trials in high-risk MDS, including one (NCT03404193) that includes high-risk CMML patients, will help to clarify the potential impact of this agent in patients with MDS/MPN.

Table 1 Active interventional clinical trials specifically assessing patients with MDS/MPN (i.e., CMML, JMML, aCML, MDS-MPN-RS-T, MDS/MPN-U)

NCT trial number	Disease state	Agent	Phase
NCT02807272	CMML	Tipifarnib	2
NCT03040401	CMML	HDC/IL-2	1/2
NCT02268253	CMML	SL-401	1/2
NCT02323178	CMML	Eltrombopag	1/2
NCT01776723	CMML	Ruxolitinib	1/2
NCT02214407	CMML	Decitabine ± hydroxyurea	3
NCT02092324	aCML	Ruxolitinib	2
NCT03190915	JMML	Trametinib	2

Outside of managing proliferative features of MDS/MPNs, treatment often focuses on improving symptoms related to anemia or thrombocytopenia. HMA therapy is typically employed to achieve these ends; however, there are some special cases in which alternative agents can be considered. Lenalidomide is established as the treatment of choice for patients with MDS with a chromosome 5q deletion [48], but has also been used to improve anemia in non-deletion 5q MDS patients and MPN patients, albeit with more modest activity [49–53]. Given the hybrid nature of MDS/MPN-RS-T, lenalidomide may be uniquely poised for efficacy in this rare disease entity and, indeed, has been shown to produce impressive responses [20, 54]. In MDS patients with disease refractory to HMA, eltrombopag has been used with limited efficacy [55]; however, it has been shown to reduce adverse events related to thrombocytopenia [56]. The experience of eltrombopag in CMML and other MDS/MPNs is limited, but it may represent an option for a specific subset of refractory, thrombocytopenic patients [8].

An improved understanding of the molecular drivers behind MDS/MPNs has allowed for targeted therapeutic approaches to be utilized in special situations. Myeloid mutation panels assist in establishing a diagnosis and, in some cases, provide guidance on therapeutic strategies. Ruxolitinib, a JAK1/2 inhibitor, is approved for use in myelofibrosis and polycythemia vera and has shown the ability to improve splenomegaly and disease-related symptoms. In MDS/MPNs, it can be used to achieve these ends, and ruxolitinib has been specifically assessed in both CMML and aCML patients. A phase 2 study of ruxolitinib in CMML demonstrated a 46% ORR with significant improvements in splenomegaly and disease-related symptoms [57•]. Similarly, a phase 2 study in patients with chronic neutrophilic leukemia (CNL) or aCML demonstrated a 37% ORR, although responses were significantly more common in patients with *CSF3R* T618I mutation which is enriched in CNL as compared with aCML. Patients with the *CSF3R* T618I mutation had a 50% ORR (10 of 20) compared with a 15% ORR in *CSF3R* wild-type patients (3 of 20). Spleen and symptom responses were again observed [58•]. Trametinib has shown some activity in aCML and CMML patients with RAS-pathway mutations [59, 60]. A general algorithm for the treatment of MDS/MPNs is illustrated in Fig. 1.

ABNL MARRO

The ABNL MARRO (A Basket study of Novel therapy for untreated MDS/MPN and Relapse/Refractory Overlap Syndromes) is an international undertaking that aims to leverage the expertise of the MDS/MPN International Working Group (IWG) research consortium in an effort to investigate novel treatment approaches in MDS/MPN. This cooperative effort will serve to streamline the development of novel

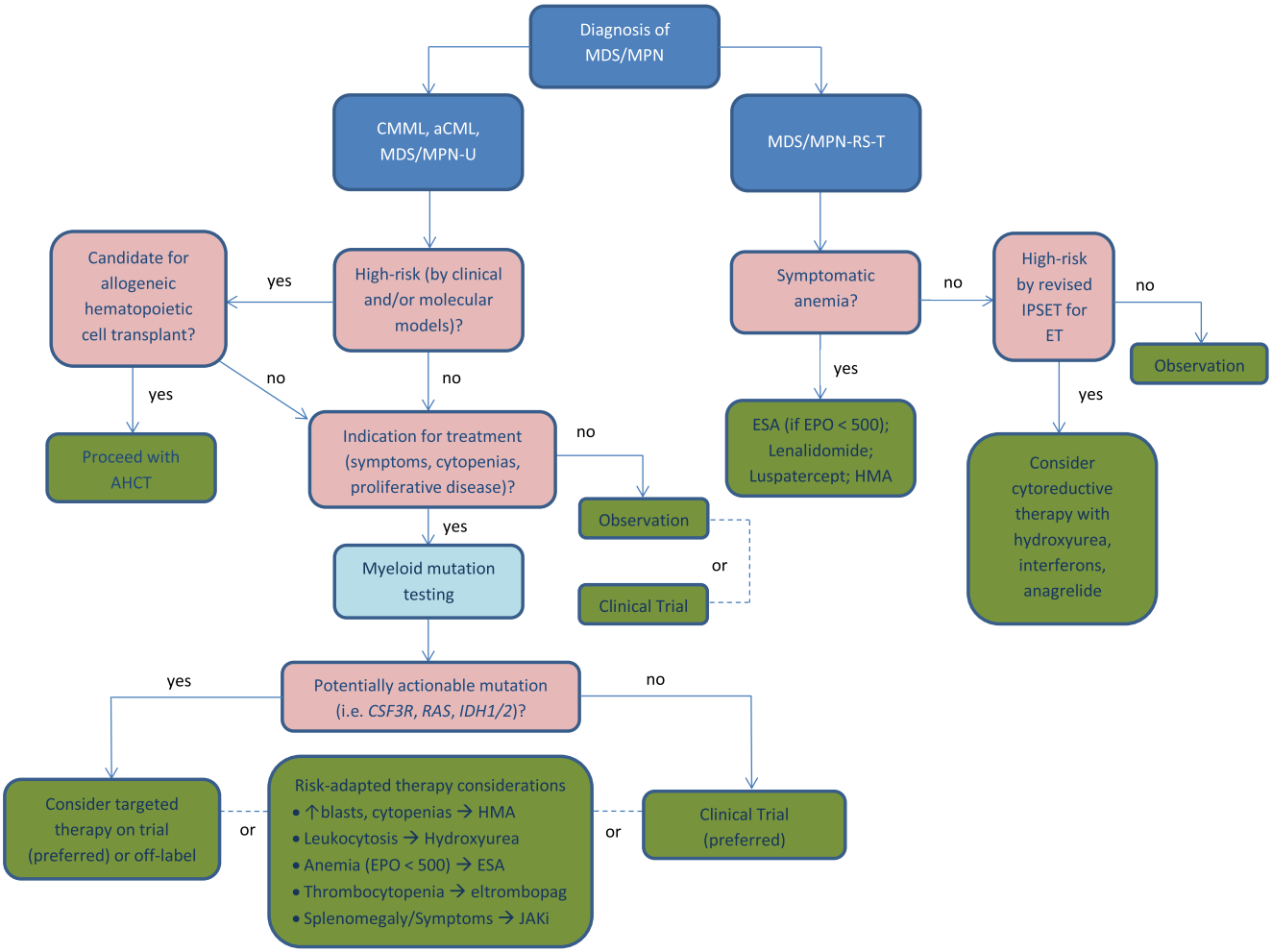

Fig 1 Proposed treatment algorithm for patients with MDS/MPN.

therapies for MDS/MPNs by running multiple interventional trials within an established, cooperative framework that aims to utilize the unique expertise of established researchers who focus heavily on MDS/MPN. The basic framework will include several exploratory phase 2 studies. ABNL MARRO-001 will start presently combining oral decitabine (ASTX 727) with 3 different targeted agents. A clinical efficacy signal will then precipitate a larger definitive study in this population. This undertaking highlights the importance of cooperation when trying to advance our understanding and treatment of rare, complex, and heterogeneous diseases.

Conclusions

MDS/MPNs represent a group of diseases with overlapping features of myeloproliferation and bone marrow failure that generally have a poor prognosis and pose a significant therapeutic challenge. AHCT remains the only therapy with curative potential; however, it carries a significant risk of morbidity and mortality. The current therapeutic landscape for MDS/MPNs continues to be largely comprised of therapies co-opted from related diseases, i.e., HMAs based on their evidence of MDS and AML; however, an improved understanding of molecular mutations which drive these diseases provides optimism for the emergence of targeted therapeutic strategies. The recent approvals of targeted agents such as enasidenib and ivosidenib in AML along with the emergence of non-chemotherapeutic agents such as venetoclax provide hope that therapeutic breakthroughs emerge from an improved understanding of disease pathobiology. The ABNL MARRO study aims to leverage this pathobiology in an effort to provide targeted therapy for MDS/MPN patients.

Compliance with Ethical Standards

Conflict of Interest Andrew T. Kuykendall and Eric Padron declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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