between the intensive and conservative blood pressure treatment groups. Despite having identical blood pressure targets, actual blood pressures were lower in both arms of ATACH-2 compared with INTERACT2, highlighting the difficulty in reproducing treatment responses across clinical trials of similar design.[11]

Well-designed neutral trials can teach us a lot. Based on the results of CLEAR III, intraventricular alteplase cannot be recommended at present for the treatment of intraventricular haemorrhage in clinical practice. However, its administration is safe and aggressive clearance of the intraventricular clot, when truly achieved, might improve morbidity and mortality. There is some support for dual simultaneous ventricular drainage catheters for patients with severe intraventricular haemorrhage.[12] More selective placement of one or more ventricular drainage catheters, with or without adjunctive thrombolysis, deserves to be investigated.

But perhaps most importantly, CLEAR III tells us that aggressive treatment of patients with intraventricular haemorrhage from intracerebral haemorrhage and good premorbid function can achieve better functional recovery than previously thought. We might not have great specific treatments for intracerebral haemorrhage or intraventricular haemorrhage, but doing what we can is still very useful.

Alejandro A Rabinstein
Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA
rabinstein.alejandro@mayo.edu

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A new therapeutic advance for symptomatic systemic mastocytosis?

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See Articles page 612

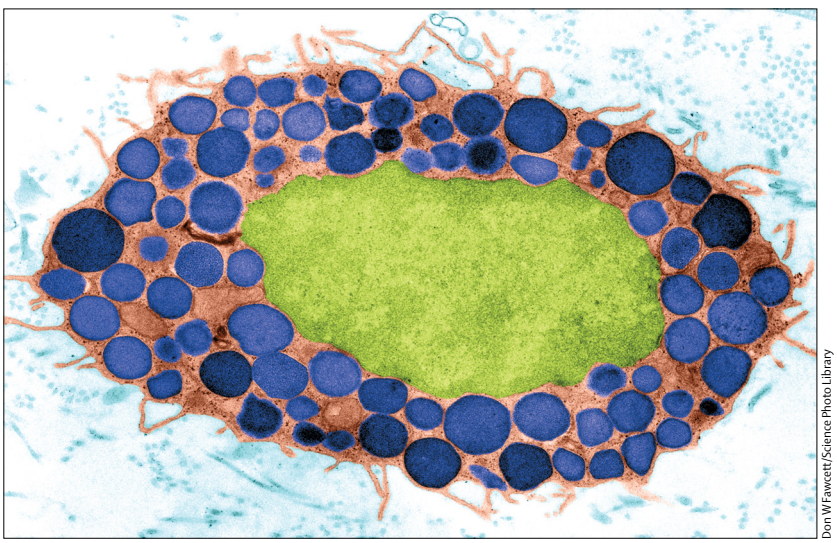
Systemic mastocytosis is a group of rare diseases characterised by accumulation of mast cells in the bone marrow or other internal organs,[1] and is classified into four major categories.[2] Indolent systemic mastocytosis is usually of good prognosis, whereas the three other categories—collectively termed advanced systemic mastocytosis—share a poorer prognosis.[3] Symptoms are related to increased release of mast cell mediators,[4] and can usually be controlled by antimediator therapies except in a subset of severely symptomatic patients.[4]

Consensus criteria for the diagnosis of systemic mastocytosis established by WHO include one major criterion— the presence of aggregates of at least 15 mast cells identified in bone marrow or other extracutaneous organ biopsies—and four minor criteria: the presence of more than 25% of mast cells with atypical morphology in bone marrow smears; aberrant immunophenotype of mast cells; presence of a point mutation in codon 816 of the *KIT* gene in bone marrow; peripheral blood or other extracutaneous organs;

and increased level of serum tryptase.[5] For diagnosis of systemic mastocytosis, at least the major and one minor criterion or at least three minor criteria are fulfilled.[5] The disease is then categorised according to the presence of B-findings (symptoms of high mast cell burden) and C-findings (signs of organ dysfunction),[5] namely absence of any findings (indolent systemic mastocytosis),[5] only B-findings (smouldering systemic mastocytosis),[6] or at least one C-finding (advanced systemic mastocytosis).[7]

Research points to KIT (a type III receptor tyrosine kinase) as a crucial player in the pathophysiology of systemic mastocytosis. Indeed, the majority of patients carry *KIT* mutations, notably KIT Asp816Val (D816V), which is found in more than 85% of all patients with systemic mastocytosis.[8] This mutation results in constitutively activated KIT, leading to aberrantly sustained proliferative and anti-apoptotic signalling in neoplastic mast cells.[8] Treatment of patients with systemic mastocytosis by targeting KIT—ie, with tyrosine kinase inhibitors (TKIs)—is therefore tempting. Unfortunately, unlike wild-type KIT, the KIT Asp816Val mutant is resistant both in vitro and in vivo to most type I TKIs, such as imatinib or masitinib, and no other TKIs can effectively cure the disease to date.[9] However, masitinib, which is effective for treating canine mastocytoma,[10] potently inhibits not only wild-type KIT but also LYN and FYN.[11] Inhibition of these two latter molecules might decrease mediator release by mast cells.[11]

In *The Lancet*, Olivier Lortholary and colleagues[12] report the positive results of a randomised, placebo-controlled, phase 3 study that included 135 severely symptomatic patients with indolent or smouldering systemic mastocytosis, who were treated with masitinib (71 patients) or placebo (64 patients). The primary endpoint was cumulative response (≥75% improvement from baseline, timeframe weeks 8–24) in at least one of four severe baseline symptoms. Masitinib showed significant improvement over placebo in its primary endpoint (18·7% cumulative response [122·6 responses of 656·5 possible responses; weighted] *vs* 7·4% cumulative response [48·9 of 656·5]; odds ratio 3·6; 95% CI 1·2–10·8; p=0·0076), regardless of KIT Asp816Val status, with long-term responses and low frequency of adverse events, with the most frequent severe adverse events being



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diarrhoea (eight [11%] of 70 in the masitinib group *vs* one [2%] of 63 in the placebo group), rash (four [6%] *vs* none), and asthenia (four [6%] *vs* one [2%]), and the most frequent serious adverse events being diarrhoea (three patients [4%] *vs* one [2%]) and urticaria (two [3%] *vs* none).[12] Therefore, the tempting conclusion reached by the authors is that "masitinib is an effective and well tolerated agent for the treatment of severely symptomatic indolent or smouldering systemic mastocytosis."

However, two points in this study deserve further discussion and investigations:

1) Although masitinib has no significant activity on KIT Asp816Val mutant, the vast majority of the patients treated were KIT Asp816Val-positive. How did masitinib improve symptoms in these patients? Most probably, masitinib might have decreased mediator release through inhibition of LYN and FYN. Although affirmed by experiments in cell lines,[11] this hypothesis has not been investigated on neoplastic mast cells from patients with systemic mastocytosis. This point deserves further investigation because the results of such experiments might lead to new concepts of treatment.

2) In the cohort of patients presented, 27 patients were not classified according to the WHO criteria, and among those, nine were classified as having systemic mastocytosis on the basis of only one criterion. This inconsistency might complicate data interpretation and direct comparison with past or future studies because it introduces the possibility of increased heterogeneity between study populations.

Despite these two points, these data offer high hopes for masitinib, which could become an attractive alternative to the therapeutic arsenal available for patients with severely symptomatic indolent or smouldering systemic mastocytosis.

Michel Arock
Molecular and Cellular Oncology, LBPA CNRS UMR 8113, Ecole Normale Supérieure de Cachan, 94235-Cachan CEDEX, and Clinical Hematology Laboratory, Pitié-Salpêtrière Hospital, Paris, France
arock@ens-cachan.fr

I declare no competing interests.

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Safety and immunogenicity of a recombinant adenovirus vector-based Ebola vaccine

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See Articles page 621

The 2013–16 epidemic of Ebola virus disease in west Africa was a game changer—not only in terms of the location and dimension of the outbreak and with regards to many painful lessons learnt about the epidemiology, features, and management of the disease, but also in terms of furthering the development of monoclonal antibody treatments[1,2] and, most importantly, vaccines. Besides the replicative vector-based rVSV-ZEBOV vaccine,[3,4] which has yielded high efficacy in an interim analysis of an open-label, cluster-randomised ring vaccination trial in Guinea,[5] a range of other candidate vaccines have progressed into clinical development. Many of these vaccines are based on non-replicative, Chimpanzee adenovirus vectors (ChAd3) or human adenovirus vectors (Ad35-EBOV, Ad26-EBOV, and Ad5-EBOV).[6]

In 2015, Feng-Cai Zhu and colleagues[7] showed safety and immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine (Ad5-EBOV), which is highly homologous with the west African outbreak strain, in a phase 1 trial of 120 healthy adults from China. Now in *The Lancet*, Zhu and colleagues[8] report the results of a randomised, double-blind, placebo-controlled, phase 2 trial, in which they assessed safety and immunogenicity of Ad5-EBOV in healthy adults in Sierra Leone who were followed up for 6 months after one injection of the vaccine. Of 500 participants, 250 were administered the high-dose vaccine ($1{\cdot}6\times10^{11}$ viral particles), 125 received the low-dose vaccine ($8{\cdot}0\times10^{10}$ viral particles), and 125 received placebo (containing only vaccine excipients, with no viral particles). Within 7 days of vaccination, solicited adverse events, which were mostly mild and self-limiting, were reported by 132 (53%) participants in the high-dose group, 60 (48%) in the low-dose group, and 54 (43%) in the placebo group. Injection-site adverse events occurred more frequently in vaccine recipients (65 [26%] in high-dose group and 31 [25%] in low-dose group) than in those receiving placebo (17 [14%]; p=0·0169). Glycoprotein-specific antibody responses were detected from day 14 (geometric mean titre 1251·0 [95% CI 976·6–1602·5] in low-dose group and 1728·4 [1459·4–2047·0] in high-dose group), peaking at day 28 (1471·8 [1151·0–1881·8] and 2043·1 [1762·4–2368·4]) and then declining rapidly (to 223·3 [148·2–336·4] and 254·2 [185·0–349·5]) at day 168.