Clinician preferences on treatment of smoldering myeloma: a cross-sectional survey

Ghulam Rehman Mohyuddin,[a,*] Rajshekhar Chakraborty,[b] Edward R. Scheffer Cliff,[c] and Benjamin A. Derman[d]

[a]Division of Hematology, Huntsman Cancer Center, University of Utah, USA
[b]Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, USA
[c]Program on Regulation, Therapeutics and Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, USA
[d]Section of Hematology/Oncology, University of Chicago, USA

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Summary

Background Smoldering myeloma (SMM) is an asymptomatic precursor condition to multiple myeloma (MM) with a variable risk of progression. The management of high-risk SMM (HR-SMM) remains controversial, particularly with changes in diagnostic criteria that led to reclassifying of some patients with SMM to MM. This study aimed to assess clinician preferences for whether to treat patients with HR-SMM and/or patients with MM diagnosed solely by SLiM criteria (free light chain ratio >100, bone marrow plasma cell percentage >60, greater than two focal marrow lesions on MRI) through an electronic survey.

Methods This was a cross-sectional survey of clinicians, conducted via an anonymous online REDCap survey from May 16th to July 5th, 2023. The survey included questions on demographics, SMM surveillance practices, and management preferences for two clinical scenarios (HR-SMM and MM based solely on the free light chain ratio >100 criterion). Data was analysed descriptively via Microsoft Excel.

Findings A total of 146 clinicians completed the full survey, with 92% recommending against routine treatment for a patient with HR-SMM based on a single time point assessment, instead preferring active surveillance. For patients with MM diagnosed solely on the basis of a free light chain ratio >100, 61% recommended active treatment, while 37% recommended active surveillance. The most common reasons recommending against treatment of HR-SMM were toxicity, lack of demonstrated overall survival benefit, and low MM-defining event rates in clinical trials.

Interpretation The survey indicates that most clinicians recommend against routine treatment for HR-SMM. Active surveillance is the prevailing standard of care and it is therefore an appropriate control arm in future SMM trials. More randomised trials are needed to determine if early treatment of modern-era SMM offers a net benefit to patients.

Funding None.

Keywords: Multiple myeloma; Smoldering myeloma; Early intervention; Randomized; Survey; Clinician preference

Introduction

Smoldering myeloma (SMM), present in one in 200 individuals over the age of 40[1], is an asymptomatic precursor condition that may or may not progress to multiple myeloma (MM). Although two randomised controlled trials have suggested that early intervention with lenalidomide may delay progression to MM for patients with high-risk SMM (HR-SMM),[2,3] these trials have major limitations that limit their applicability to current clinical practice.[4,5] Thus, whether early treatment of patients with modern-era SMM offers a true benefit remains unknown, although it may come with financial toxicity and/or side effects.[6,7] Some experts recommend treatment with lenalidomide for patients with HR-SMM,[8,9] while others recommend close observation.[10]

Changes to the International Myeloma Working Group diagnostic criteria in 2014 led to reclassification of patients with the highest-risk SMM to MM in an attempt to avert development of irreversible morbidity despite their lack of symptomatic disease.[4,11] These 'SLiM' criteria reclassified as MM anyone with any of:

*Corresponding author. Huntsman Cancer Institute, University of Utah, 1950 Circle of Hope Drive, Salt Lake City, UT, 84106, USA.
E-mail address: g.mohyuddin@hci.utah.edu (G.R. Mohyuddin).

Research in context

Evidence before this study

We searched Google Scholar, Web of Science, and PubMed for studies on July 15th 2023 with the combination of the following terms: "smoldering myeloma", and "randomised" or "randomized". We found two randomised trials that suggest a potential benefit to early treatment with lenalidomide for patients with high-risk smoldering myeloma, although these trials both have major limitations that limit their applicability to practice today. Despite these two randomised trials, and some guidelines that advocate for the treatment of high-risk smoldering myeloma, controversy remains surrounding its management. Although the clinical and financial toxicity of treatment are well known, it remains unknown whether patients with high-risk smoldering myeloma in the modern era live longer or better with early intervention.

Added value of this study

To our knowledge, this is the first international survey to assess clinician preferences in treating high-risk smoldering myeloma in the modern era. We surveyed 146 clinicians, and demonstrate that 92% of them recommend against treating high-risk smoldering myeloma. This runs contrary to some current guidelines that recommend treatment of HR-SMM, as well as current randomised trials in which the patients in the control arm receive active treatment. Our data indicates that the current level of evidence to support early intervention in high-risk smoldering myeloma is insufficient to convince the majority of clinicians that early intervention offers a net benefit to patients.

Implications of all the available evidence

Our findings suggest that active surveillance is the prevailing standard of care approach among myeloma clinicians and is therefore a reasonable control arm for future high-risk smoldering myeloma trials. Furthermore, the fundamental question of whether or not to treat smoldering myeloma remains unanswered, and future trials should address this by assessing clinical endpoints such as quality of life and overall survival.

(1) more than one focal marrow lesion on magnetic resonance imaging (MRI), (2) bone marrow plasma cells ≥60%, or (3) a serum free light chain ratio ≥100.[4] These patients' disease was recharacterised as MM because they were estimated to have an 80% risk of progression to MM two years after diagnosis.[4] Due to the heterogeneity in enrolment criteria and imaging modalities utilised,[6,12] in addition to the introduction of the SLiM criteria and resulting reclassification, it is difficult to extrapolate results from trials that enrolled patients with SMM prior to 2014. Furthermore, whether all patients who meet SLiM criteria for the diagnosis of MM should be routinely treated is also controversial, as recent data has shown that the two-year risk of progression to MM may be much lower than 80%.[13,14]

Controversy thus remains as to whether HR-SMM should be routinely treated or not. Despite this controversy, there are no ongoing randomised trials today enrolling patients with HR-SMM that allow for observation as a control arm.[15] There is thus an urgent need to assess clinician preferences in this area to shape both guidelines and trial design. Using an electronic survey, this study assessed clinician preferences on treating patients with HR-SMM and patients with MM by SLiM criteria only, by asking management preferences for two clinical scenarios.

Methods

Study design

An anonymous online REDCap survey was distributed to clinicians who see patients with MM and SMM via social media, email lists and online forums between May 16th and July 5th, 2023. The survey was approved by the University of Chicago institutional review board (Supplement).

Procedures

This cross-sectional survey included questions on demographics, clinician recommendations on SMM surveillance (tests performed and their frequency), as well as questions regarding clinical scenarios and progression risk thresholds at which treatment would be considered. This survey was not formally pre-tested, and no specific assumptions were made regarding the results prior to survey deployment that would require a sample size calculation. Participation in this survey was voluntary with no reimbursement offered, and all answers were confidential.

In brief, the clinical scenarios included the following:

1. 'HR-SMM scenario': A patient with HR-SMM according to the Mayo 2/20/20 criteria,[16,17] with a monoclonal protein spike of 2.3 g/dL (23 g/L), bone marrow monoclonal plasma cell percentage of 30%, and involved/uninvolved free light chain ratio of 30. This patient had a negative diffusion-weighted whole body myeloma MRI indicating no focal lesions, and no end-organ damage attributable to MM.
2. 'SLiM based on light chain ratio scenario': A patient with MM according to the IMWG 2014 updated criteria,[4] based on a free light chain ratio of 108. This patient had a negative diffusion-weighted whole body myeloma MRI indicating no focal lesions, and no end-organ damage attributable to MM.

For both scenarios, it was assumed that no clinical trial was available for participation.

Outcomes

There were two primary objectives of this survey: firstly, to ascertain what proportion of respondents would recommend treatment for a patient diagnosed with HR-SMM, and secondly to ascertain what proportion of respondents would recommend treatment for a patient diagnosed with MM based only on light chain ratio.

Statistical analysis

Statistical analyses were performed using Microsoft Excel (Microsoft Corporation, 2018) by two authors (GRM & BD). Results were analysed descriptively, with no formal statistical tests performed to compare respondents. The Consensus-Based Checklist for Reporting of Survey Studies (CROSS) checklist was adhered to.[18]

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and accept full responsibility for the decision to submit for publication.

Results

Two hundred and forty-four respondents agreed to participate, 180 (180/244, 74%) of whom completed demographic information, and 146 (146/244, 60%) of whom provided sufficiently complete answers to form the basis of this analysis. Self-identified academic clinicians were 66% of respondents (96/146), as opposed to those in private practice or hybrid setting (50/146, 34%). A majority of participants were from North America (57%), followed by Europe (26%). Participant demographics are listed in Table 1.

Demographic Information	Participants who completed entire survey (n = 146)	Participants who answered information on demographics (n = 180)
Academic Practice	103, 71%	124, 69%
Community/Hybrid Practice	43, 29%	56, 31%
North America	82, 56%	100, 56%
Europe	37, 25%	46, 26%
South America	11, 8%	13, 7%
Australasia	9, 6%	9, 5%
Asia	6, 4%	8, 4%
Africa	1, 1%	4, 2%
Patients with MM seen per week (median, interquartile range)	10, 14	10, 15
Years in practice (median, interquartile range)	10, 14	10, 13

Table 1: **Demographics of survey respondents.**

Guideline usage

The most commonly used clinical practice guidelines were those from the National Comprehensive Cancer Network (NCCN) (80/146, 55%), followed by UpToDate (56/146, 38%), mSMART (49/146, 34%), and European Society of Medical Oncology (ESMO) (29/146, 20%). Fifty-four participants (54/146, 37%) had previously enrolled a patient with SMM to a clinical trial.

Diagnostic workup

Serum protein electrophoresis/immunofixation was included in 141 (141/146, 97%) of participants' SMM evaluation, and serum free light chain assessment in 139 (139/146, 95%). A total of 89 (89/146, 61%) participants reported using urine electrophoresis/immunofixation in their assessment of SMM.

Most participants used advanced imaging during their evaluation of patients with SMM; most commonly PET/CT (92/146, 63%), whole-body CT (49/146, 34%), MRI spine/pelvis (33/146, 23%), and MRI whole body (n = 32, 22%). Notably, only 24 (16%) respondents used skeletal survey. Most participants (129, 88%) included bone marrow biopsy and aspiration as part of their diagnostic workup.

Follow-up of HR-SMM

Of the 133 participants who responded to questions regarding frequency of imaging and lab surveillance of HR-SMM, 52 (52/133, 39%) recommended 12-monthly imaging, 29 (29/133, 22%) every 6 months, one (1/133, 1%) did not recommend surveillance imaging, and 46 (46/133, 35%) only recommend imaging if there is clinical suspicion for progression. Five respondents (5/133, 4%) recommended other imaging frequencies.

In the first year of follow-up, 92/133 (69%) recommended lab surveillance every three months, 26 (26/133, 20%) recommended lab surveillance monthly, and 15 (15/133, 11%) respondents recommended lab surveillance at other frequencies.

Risk stratification scores

The most used risk stratification model for SMM in practice was the Mayo Clinic 2/20/20 model (99/146, 68%),[16] followed by the IMWG SMM score[17] (63/146, 43%), the PANGEA score[19] (24/146, 16%), PETHEMA (12/146, 8%), and the Mayo 2008 model (8/146, 5%).[20] A total of 16 (16/146, 11%) participants indicated they do not use any of these risk stratification scores in practice.

SMM treatment preferences and reasoning

Outside of a clinical trial, 133/146 (92%) participants recommend against treatment for HR-SMM based on a single time point assessment. The most common reasons for not recommending treatment were toxicity of treatment (100/146, 68%), lack of demonstrated overall survival benefit (99/146, 68%), low rates of MM-defining events in clinical trial control groups (42/146, 29%),

concern about resistance to drugs (37/146, 25%), and lack of deep response with available therapies (19/146, 13%). Some participants expressed concerns about the ability to collect stem cells (13/146, 9%).

Among the 13 (8%) clinicians recommending treatment of HR-SMM, reasons to do so included prevention of irreversible end-organ damage (9/13, 69%), curing MM at its inception (2/13, 15%), improving progression-free survival (5/13, 38%), and improving quality of life and decreasing anxiety (1/13, 8%).

Clinical scenarios

146 participants answered the clinical scenario questions. Regarding the patient with HR-SMM, 134 participants (134/146, 92%) recommended active surveillance/observation, nine (9/146, 6%) recommended treatment with lenalidomide with or without dexamethasone, and three (2/146, 2%) recommended other treatment options (Fig. 1).

The second clinical scenario was correctly identified as MM based on SLiM criteria by 118/146 participants (81%), whereas 27 participants (18%) incorrectly identified the patient as having SMM. Among 145 participants who provided a management recommendation, 88 (88/145, 61%) recommended MM therapy (triplet or quadruplet induction ± autologous stem cell transplant), whereas 52 (52/145, 37%) participants recommended active surveillance, and five participants (3%) recommended lenalidomide alone. Amongst 27 participants (27/146, 18%) who incorrectly diagnosed this case as SMM, 18 (18/27, 66%) recommended observation.

Risk of progression warranting treatment

Clinicians were asked to indicate the 2-year risk of progression to MM at which they would consider recommending treatment for SMM (Fig. 2). Forty-nine respondents (49/146, 34%) stated that a 2-year risk of progression of at least 80% would be required to recommend treatment, and 31% would not recommend treatment unless criteria for MM were met.

Discussion

This survey demonstrates that over 90% of participating clinicians recommend against routine treatment of HR-SMM based on a single time point assessment, instead preferring active surveillance. The majority of participants correctly applied the 2014 diagnostic changes that classify some patients with MM in the absence of symptoms; while 61% recommended active treatment of a patient meeting MM criteria based on a free light chain ratio of >100, over a third of participants recommended active surveillance even in this scenario. Despite the lower contemporary risk of progression for patients diagnosed with MM based only on a free light chain ratio of >100 than originally thought in 2014,[13] most clinicians still recommend routine treatment of such patients.

Our results suggest very few clinicians recommend treatment with lenalidomide for HR-SMM, despite two randomised trials suggesting a lower risk of progression to MM in patient populations previously defined as HR-SMM. This is likely because of the limitations of those studies. The QuiRedex trial began enrollment in 2007,

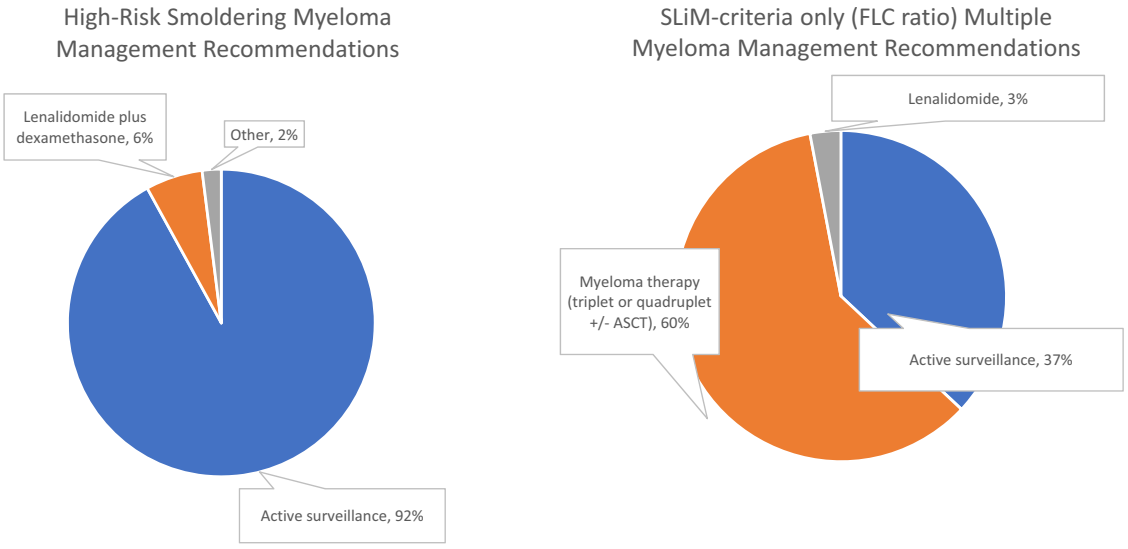

Fig. 1: **Management of high-risk smoldering myeloma and SLiM-criteria only myeloma (based on free light chain ratio only) by survey respondents**. Blue represents those who recommended active surveillance rather than treatment.

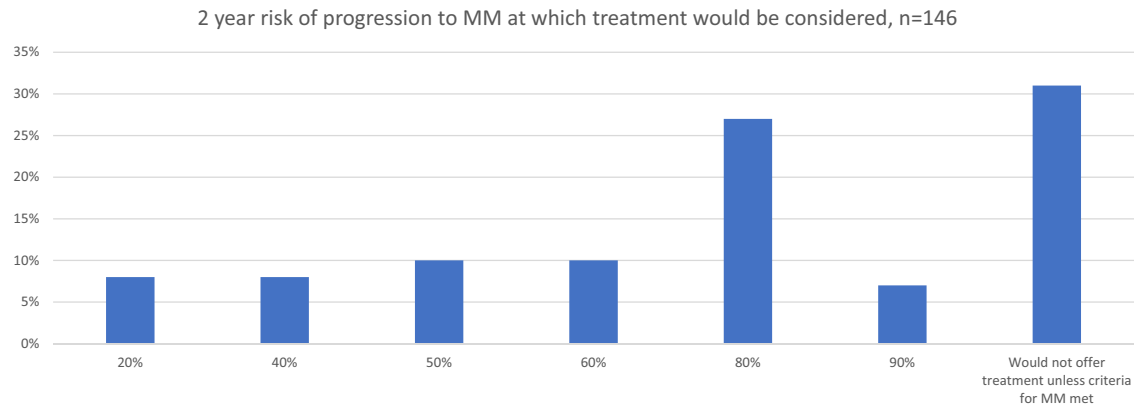

Fig. 2: **Participant responses of what threshold of two-year risk of progression to multiple myeloma would warrant treatment for a patient with smoldering myeloma**. Different risk of progression thresholds on X axis, percentage of respondents on Y axis.

prior to both the use of advanced imaging techniques and diagnostic reclassification of MM.[3] Consequently, a substantial number of participants in this trial would likely be diagnosed with MM today. While an overall survival (OS) benefit was shown for those receiving lenalidomide and dexamethasone, this trial was not powered for OS analysis, and lenalidomide was received by only 28% of patients in the control arm upon progression to MM.[21] The E3A06 trial enrolled only a minority of patients with HR-SMM, was also not powered to assess OS, did not characterise the exact nature of progression events, and at latest reported follow-up (three years), approximately 70% of patients in the observation arm had not progressed.[2] Furthermore, cross-over to lenalidomide prior to formal progression to symptomatic MM limits the interpretation of OS in this study. Additionally, during the safety run-in phase of the study, one patient developed a secondary hematologic malignancy, highlighting the potential risks of early intervention.[22] Despite these two trials, controversy remains surrounding the management of SMM, and further trials of patients with SMM defined by modern criteria, powered for clinical endpoints such as OS and quality of life, are needed to show whether early treatment of modern-day SMM is indeed beneficial. Furthermore, the lack of a unique billing or reimbursement code for SMM largely precludes the use of either insurance claims data or aggregated electronic health record data to distinguish patients with SMM from those with MM and therefore to evaluate the prevailing standard of care for SMM.

A recent population-based prospective screening study from Iceland (iSTOPMM) has shown that 1 in every 200 people amongst the general population have SMM.[1] Our understanding of SMM and recommendations on its diagnosis and prognostication come from studies that have looked at SMM diagnosed in a clinical setting (as opposed to screening), and prior to diagnostic reclassifications and use of advanced imaging.[23] It is likely that contemporary patients with SMM (especially those who may be picked up due to screening and/or expanded use of highly sensitive assays[24]) have an even lower risk of progression, and thus a lower potential benefit of treatment compared to earlier studies.

Current risk stratification models for SMM are varied and lack both concordance and prospective validation, limiting their applicability to clinical practice.[14,25] Some of these models were derived from older datasets predating the routine use of advanced imaging and diagnostic reclassifications, which may explain why some models may overpredict the risk of progression to MM. Although we found that the Mayo 2/20/20 model was used most often, likely due to its convenience,[16] there remains no clear standard model for use in clinical practice. It is very likely that characteristics of contemporary SMM patients differ dramatically from the dataset from which the Mayo 2/20/20 model was derived.[16] For example, patients with SMM identified on the iSTOPMM study had a median monoclonal protein of 0.62 g/dL, in contrast to a median monoclonal protein of 2 g/dL in the Mayo cohort.[1,16]

Most participants described concerns regarding toxicity and lack of demonstrated overall survival benefit as reasons for not recommending treatment of HR-SMM. Only five participants considered improvement in progression-free survival as sufficient justification for recommending treatment with HR-SMM. This highlights the inadequacy of progression-free survival as an informative endpoint in this scenario; ultimately, patients and clinicians want to know the optimal timing of using effective anti-myeloma drugs, and whether early initiation offers greater benefits than it does risks, so trials should be designed to answer this question.[26] Given that most ongoing SMM clinical trials use surrogate endpoints,[12,15] these findings raise concern for the design of current trials. Furthermore, there are no

randomised trials enrolling currently for HR-SMM that offer observation or active surveillance as a control arm.[15] Our study highlights that there is sufficient equipoise among treating clinicians to justify active surveillance as a control arm, as the prevailing standard of care for modern SMM patients is in fact active surveillance.

We also demonstrate that advanced imaging is utilised by most clinicians, as opposed to skeletal survey. Use of advanced imaging is recommended by contemporary guidelines,[27] as a skeletal survey can miss up to 40% of lytic lesions that can be picked up by modalities such as whole-body diffusion weighted MRI or PET/CT.[28,29] Widespread use of these modalities can reclassify patients as having MM who would otherwise have been diagnosed as SMM based on a negative skeletal survey.[5] However, the use of MRI was less common than PET/CT, and as the detection of focal bone marrow lesions on MRI is a MM defining event,[4] these findings have important implications for clinical practice. Increased use of MRI may lead to further patients with SMM being reclassified to MM.

Limitations of this survey include that it may not be representative of practice patterns globally, as most participants were from North America and worked at academic institutions. The use of social media as a recruitment mechanism may limit its representativeness, and some participants did not complete the survey despite consenting to participation. This may represent selection bias; it could have been that those more likely to challenge existing guidelines and recommendations were more likely to fill out the survey. This limitation could be addressed by future surveys systematically deployed globally at cancer centres with accurate measurement of survey completion rates amongst all those whom the survey was offered to. This survey of clinician preferences does not assess individual patient values and preferences, and treatment recommendations may be tailored to suit each patient and their priorities. Furthermore, although over a third of participants recommended observation for patients diagnosed with MM based on a light chain ratio of >100, one third of these clinicians may have suggested observation due to incorrectly diagnosing this patient as having SMM. Another limitation is that the survey was open for a short period of time (May 16th–July 5th 2023), which may have limited responses. As responses began to diminish towards the latter part of the study period despite reminders, with very few survey respondents in the last week the survey was open, which led to the decision to close the survey.

Our study highlights that the vast majority of respondents recommend against treatment of HR-SMM. Furthermore, over a third of participating clinicians also recommend active surveillance for MM diagnosed solely on the basis of a free light chain ratio of >100. Our data indicates that the current level of evidence to support early intervention in HR-SMM is insufficient to convince the majority of clinicians that early intervention offers a net benefit to patients. As such, active surveillance is the prevailing standard of care approach among treating clinicians and is therefore a reasonable control arm in future SMM trials.

Contributors

All authors conceived the idea for the study. GRM devised the first draft of the survey, which was closely reviewed and edited by RC, EC and BD. BD sought IRB approval, deployed the survey on RedCap and created the shareable survey link. GRM and BD performed analysis of the results and verified the data. GRM wrote the first draft of the manuscript, which was closely reviewed and edited by RC, ED and BD. All authors had full access to all the data in the study and accept full responsibility for the decision to submit for publication.

Data sharing statement

The data for this study may be shared upon reasonable request to the corresponding author.

Declaration of interests

GRM has received royalties from MashupMD for writing. He declares no conflicts of interest with pharmaceutical companies or any that are relevant to this work. EC receives research funding from Arnold Ventures. RC has consulted for Sanofi, Janssen and Adaptive, and received research funding from Abbvie. BD reports consulting for Janssen, Sanofi, COTA, Inc, Multiple Myeloma Research Foundating and Plexus communication, as well as serving on a data safety monitoring committee for BMS.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102272.

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