Mobilization in myeloma revisited: IMWG consensus perspectives on stem cell collection following initial therapy with thalidomide-, lenalidomide-, or bortezomib-containing regimens

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The past decade has witnessed a paradigm shift in the initial treatment of multiple myeloma with the introduction of novel agents such as thalidomide, lenalidomide, and bortezomib, leading to improved outcomes. High-dose therapy and autologous stem cell transplantation remains an important therapeutic option for patients with multiple myeloma eligible for the procedure. Before the advent of the novel agents, patients underwent stem cell collection prior to significant alkylating agent exposure, given its potential deleterious effect on stem cell collection. With increasing use of the novel agents in the upfront setting, several reports have emerged raising concerns about their impact on the ability to collect stem cells. An expert panel of the International Myeloma Working Group (IMWG) was convened to examine the implications of these therapies on stem collection in patients with myeloma and to develop recommendations for addressing these issues. Here we summarize the currently available data and present our perspective on the problem and potential options to overcome this problem. Specifically, we recommend early mobilization of stem cells, preferably within the first 4 cycles of initial therapy, in patients treated with novel agents and encourage participation in clinical trials evaluating novel approaches to stem cell mobilization. (Blood. 2009;114:1729-1735)

High-dose therapy and autologous stem cell transplantation for multiple myeloma

High-dose therapy and autologous stem cell transplantation (ASCT) remains an integral component of the myeloma treatment algorithm for patients considered eligible for the procedure. The majority of the randomized clinical trials have demonstrated a superior progression-free survival among patients undergoing ASCT compared with those treated with only conventional therapies and ASCT was associated with superior overall survival in 3 of those.[1-7] Subsequent randomized trials have further defined the role of ASCT by demonstrating equivalent overall survival for delayed transplantation compared with upfront ASCT, albeit with some compromise in the quality-of-life parameters.[8] Introduction of novel agents such as thalidomide, lenalidomide, and bortezomib have resulted in a

paradigm change in the therapy of myeloma.[9-14] The high response rates with these agents, hitherto seen only in the context of high-dose therapy, have once again raised questions regarding the utility of ASCT in the setting of myeloma. Given the lack of long-term follow-up of patients treated with these new agents, the durability of these responses as well as their potential long-term adverse effects remain unknown and ASCT continues to be an important part of myeloma therapy.

Despite the increased use of the newer drugs for the initial treatment of myeloma, there is a continuous increase in the number of ASCTs reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), highlighting their continued important role. Currently, the novel agents appear best suited to be used as first-line therapy, enhancing the quality of responses prior to proceeding to ASCT and diminishing early mortality from

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the disease, or in selected patients as primary therapy, moving ASCT to a second-line position or as adjuncts to transplant conditioning regimens or as maintenance therapy in patients undergoing ASCT.[15-23] Furthermore, in a randomized trial evaluating single versus double ASCT a survival advantage with tandem ASCT was demonstrated in an unplanned subset analysis for those patients not obtaining at least a very good partial response after the first ASCT. This observation has increased the number of ASCTs being performed for patients not achieving very good partial response after the first ASCT.[24] In addition, ASCT can also be used as part of second-line therapy after relapse, especially among patients who achieved a durable response after the first ASCT.[6,23]

The traditional approach to patients with newly diagnosed myeloma, considered to be candidates for ASCT, has been to provide initial therapy with 4 to 6 cycles of a non–alkylator-containing regimen followed by collection of stem cells and high-dose therapy. The initial therapy for the disease allows time to obtain necessary insurance approvals as well as control disease-related symptoms, simultaneously controlling toxicity by limiting the number of cycles. In addition, adequate disease control provides an opportunity to reverse disease-related complications where feasible, and generally improve the functional status of the patient, allowing for a safer transplantation. Until the advent of the novel agents, the initial therapy regimens commonly used were vincristine, doxorubicin, and dexamethasone (VAD) or single-agent dexamethasone, both of which shared the advantage of having little impact stem cell mobilization and collection. Previous studies had shown that alkylating agents can potentially affect the stem cell pool and thus interfere with the ability to collect adequate numbers of stem cells.[25-28]

The number of CD34$^+$ cells collected for ASCT is dependent on a number of factors, most importantly the number of intended transplantations. The cell collection target usually depends on patient age, upfront versus delayed ASCT, patient preference, patient performance status, and presence of comorbidities, among others. Traditionally, the target for CD34 cell collection for a single ASCT has been 4 to 6 × 10^6 CD34$^+$/kg, with studies showing a deleterious impact on engraftment characteristics once the number falls below 2 × 10^6 CD34$^+$/kg.[29,30] Use of more CD34 cells has not been consistently associated with any significant benefit in the parameters studied. Patient age is an important factor from several perspectives. Clearly there is decreasing use of stem cell transplantation (SCT) with increasing patient age, although selected patients with good performance status may undergo transplantation into their mid-70s. The target for stem cell collection is usually based on single transplantation in the United States, because Medicare reimburses only single SCT for myeloma. Finally, there is a clear impact of age on the ability to collect stem cells, with decreasing yield with advancing age.[31] In the majority of patients undergoing an ASCT for myeloma, stem cells are collected from the peripheral blood following mobilization using growth factor administration with or with out preceding chemotherapy. A minority of patients undergo ASCT with stem cells collected through a bone marrow harvest. Use of cyclophosphamide or other chemotherapy regimens for myelosuppression to achieve rebound CD34$^+$ cell spillover into the blood with enhanced effects of myeloid growth factors during the recovery phase of peripheral blood counts allows for a more rapid stem cell collection and higher numbers of collected CD34$^+$ cells compared with myeloid growth factor alone.[32-35] Institutions differ in their standard approach for collecting stem cells, with pros

and cons to either approach. Use of cyclophosphamide, although allowing better stem cell collection and less likelihood of a collection failure (less than the 2 × 10^6 CD34$^+$/kg), prolongs the collection process while awaiting count recovery and increases the risk of febrile neutropenia and other infectious complications.

One of the recent advances in the field of stem cell mobilization strategies has been the introduction of AMD3100 (plerixafor), a receptor chemokine receptor 4 (CXCR4) inhibitor. Previous studies have highlighted the role of CXCR4 in the stem cell mobilization induced by granulocyte colony-stimulating factor (G-CSF) and cyclophosphamide. Lévesque et al showed that mobilization of stem cells by G-CSF coincides in vivo with the cleavage of the N-terminus of the chemokine receptor CXCR4 on the stem cells in the BM, leading to loss of chemotaxis in response to the CXCR4 ligand, the chemokine stromal cell–derived factor-1 (SDF-1/CXCL12).[36] In addition, accumulation of serine proteases led to cleavage and inactivation of SDF-1. Originally developed as an anti-HIV drug, the ability of this drug to enhance peripheral mobilization of CD34$^+$ cells was subsequently recognized. AMD3100, a reversible inhibitor of the binding of stromal cell–derived factor-1α (SDF-1α, also known as CXCL12) to its cognate CXCR4, has been shown to increase the number of circulating CD34$^+$ cells in healthy volunteers when administered alone or with G-CSF prior to treatment.[37-39] Stem cells express CXCR4 and are known to migrate to the bone marrow through a chemoattractant effect of SDF-1α that is produced locally by bone marrow stromal cells. Once in the marrow, it is also believed that stem cell CXCR4 can act to help "anchor" these cells to stromal cell surface SDF-1α. AMD3100-induced leukocytosis and elevations in circulating hematopoietic progenitor cell levels are thought to result from a disruption of the CXCR4/CXCL12 interaction and cell adhesion effects, resulting in the appearance of both mature and pluripotent cells in the systemic circulation. AMD3100 has been shown to exert an additive effect on the number of circulating hematopoietic stem and progenitor cells when administered with G-CSF. AMD3100-3102 was a multicenter randomized, double-blind, placebo-controlled comparative trial designed to examine the ability of 240 µg/kg AMD3100 plus G-CSF versus placebo plus G-CSF to mobilize CD34$^+$ stem cells in patients with multiple myeloma (MM), who had not previously failed stem cell collections and had not received previous stem cell transplant. The primary end point, the percentage of patients who achieved 6 × 10^6 or more CD34$^+$ cells/kg in 2 or fewer apheresis days, was met in 106 (72%) of 128 patients in the AMD plus G-CSF group and 53 (34%) of 154 patients in the placebo plus G-CSF group, ($P < .001$). Fifty-four percent of study patients reached target after 1 day of apheresis in the AMD + G-CSF group compared with 17.3% in the placebo plus G-CSF group. After 4 days of apheresis, these numbers were 86.8% and 56%, respectively.[40]

Thalidomide-, lenalidomide-, or bortezomib-based regimens as initial therapy for multiple myeloma

Introduction of thalidomide represented the first major therapeutic advance in myeloma in several decades. After the initial trials in relapsed myeloma, several randomized phase 3 trials of thalidomide and dexamethasone in patients with previously untreated myeloma were performed.[15,18,41,42] Thalidomide combinations were associated with superior response rates and improved response

Table 1. Studies of novel agents with data available for success of stem cell collection

Reference	Treatment regimen	No.	Clinical trial	Mobilization regimen	CD34 yield, $\times 10^6$/kg	P	Days of leukapheresis	Failed collection % (definition)
Breitkreutz et al[54]	TAD	93	Phase 3	CAD	9.8 (2-33.6)	.02	1 (1-6)	4 ($< 2.5 \times 10^6$/kg)
	VAD	105	(GMMG-HD3)		10.9 (3-36)		1 (1-7)	7
Breitkreutz et al[54]	TAD	100	Phase 3 (HOVON-50)	CAD	7.4 (2-33)	.009	1 (1-4)	3 ($< 2.5 \times 10^6$/kg)
	VAD	100			9.4 (0-48.7)		1 (1-4)	5
Rajkumar et al[15]*	TD	99	Phase 3 (E1A00)	Various	NA	NA	NA	10 (NA)
	D	100					NA	10
Cavo et al[18]	TD	100	Matched pair analysis	CTX + G-CSF	7.85	.4	2	17 ($< 4 \times 10^6$/kg)
	VAD	100			10.5		2	12
Kumar et al[33]	Dex	78	Retrospective	G-CSF	9.6 (1-18)	< .01	3 (1–10)	1 ($< 2.5 \times 10^6$/kg)
	VAD	22			9.8 (2.1-16.2)		4 (2–10)	1
	TD	99			10.0 (3.5-30.1)		4 (1–10)	0
	LD	43			7.9 (0-15.6)		5 (1–12)	3
Mazumder et al[55]	LD	28	Retrospective	G-CSF	5.4 (0-17.5)	NA	NA	43 ($< 2 \times 10^6$/kg)
Paripati et al[56]	Other	41	Retrospective	G-CSF	7.4	.003		7.3 ($< 2 \times 10^6$/kg)
	LD	20			5.1			45
Rajkumar et al[12]†	LD	223	Phase 3 (E4A03)	Various	NA	NA		3 (NA)
	Ld	220			NA			3 (NA)
Kumar et al[57]	LD/Ld	92	Retrospective	G-CSF	7.9 (0-16)	NA		11 ($< 2.5 \times 10^6$/kg)
		11		CTX + G-CSF	8.6 (0-21)			
Mark et al[58]	BiRD	9	Retrospective	G-CSF	3.1 (0.2-8.6)	< .01		3 ($< 4 \times 10^6$/kg)
		19		CTX + G-CSF	14.2 (4.9-236)			0
Cook et al[59]	LD	21	Retrospective	CTX + G-CSF	6.3 (2.4-19.7)		3 (1-8)	9 ($< 2.5 \times 10^6$/kg)
		137		(4 with G-CSF $\pm$ AMD3100)	7.3 (2.4-72.5)		2 (1-11)	1.5
Popat et al[60]	LD	64	Retrospective	G-CSF	NA			25 ($< 2 \times 10^6$/kg in 4 days)
	Other	238						4
Jagannath et al[21]	BD	8			13·20 (7·2-16·1)		2 (2-3)	0
Harousseau et al[17]	BD	240	Phase 3	G-CSF	6.8		2.0 (mean)	4 ($< 2 \times 10^6$/kg)
	VAD	242	(IFM 2005-01)		8.4		1.6 (mean)	2
Sonneveld et al[20]	BAD	150	HOVON-65	CTX + G-CSF	10.48 (4-37)		1 (1-5)	
	VAD	150			9.26 (4.1-37.6)		1 (1-4)	
Richardson et al[51]	VRD	23	Phase 2	GCSF	6.2			8.7

TAD indicates thalidomide, doxorubicin, and dexamethasone; VAD, vincristine, doxorubicin, and dexamethasone; CAD, cyclophosphamide 1 g/m² per day, iv, on day 1; doxorubicin 15 mg/m² per day, iv, on days 1 to 4; dexamethasone 40 mg orally, days 1-4, and granulocyte colony-stimulating factor (G-CSF); NA, not available; TD, thalidomide, dexamethasone; CTX, cyclophosphamide; LD, lenalidomide, dexamethasone; Ld, lenalidomide and weekly dexamethasone; and BD, bortezomib and dexamethasone.

*Information on whether a stem cell harvest was attempted was available only for 79% of patients, among whom 37% attempted stem cell harvest. Collection details were not available.

†Details of stem cell collection regarding cell counts and definition of failure were not available and are likely to represent a mix of practices given the multicenter nature of trial.

duration with no definite impact on the overall survival compared with dexamethasone alone or VAD. This was followed by introduction of the thalidomide analog, lenalidomide, that in phase 2 trials resulted in very high response rates as well as deeper responses than were seen with previous approaches.[11,43] Subsequent phase 3 trials of lenalidomide and dexamethasone demonstrated its superiority compared with dexamethasone alone as well as its ability to spare high doses of steroids and simultaneously improve survival.[12,19] More recent clinical trials have examined the efficacy and tolerability of lenalidomide combined with cyclophosphamide (CTX), bortezomib, and clarithromycin, as well as other combinations.[44-46] Another major advance in the field had been the introduction of the proteasome inhibitor bortezomib, which along with dexamethasone or in combination with conventional chemotherapy agents is increasingly being used in the setting of newly diagnosed disease with high efficacy. Phase 3 trials of bortezomib in combination with dexamethasone with or without doxorubicin has shown excellent tolerability and improved response rates and progression-free survival compared with traditional VAD in the setting of initial therapy prior to SCT.[17,20,47] Both lenalidomide and bortezomib have been combined with cyclophosphamide in the setting of transplantation-eligible patients in phase 2 studies with

excellent response rates.[48,49] Recently reported phase 2 trials have examined the efficacy of combining bortezomib with lenalidomide or thalidomide with or without cyclophosphamide in the setting of newly diagnosed MM.[50-53] These combinations have led to very high complete and very good partial response rates and will undoubtedly become integral components of the initial treatment choices in the future. This in turn has led to renewed interest in the potential impact of initial therapy on the ability to collect adequate numbers of stem cells for one or more transplantations.

Impact of thalidomide, lenalidomide, and bortezomib on peripheral blood stem cell collection

A large volume of data, albeit limited to single institution reports and less detailed data from phase 3 trials, has appeared in the past few years evaluating the effect of these new drugs on the stem cell collection process (Table 1). Although there are contradictory data on the impact of thalidomide on stem cell mobilization and collection, the effect if any appears to be relatively small with

limited impact on the ability to proceed with SCT.[15,18,33,54] In addition, there is no evidence to suggest that initial therapy with thalidomide-containing regimens prior to stem cell collection adversely impacts the engraftment potential of the collected stem cells.

In contrast to thalidomide, one of the common adverse effects of lenalidomide has been hematologic toxicity, especially myelosuppression. This finding raised concern that use of lenalidomide could adversely affect the ability to mobilize and collect adequate numbers of CD34$^+$ cells for ASCT. In 2 large studies from Mayo Clinic and M. D. Anderson, the most significant factor influencing the ability to collect adequate numbers of stem cells appeared to be initial therapy with lenalidomide (Table 1).[33,60] In addition to lenalidomide therapy, other important factors impacting the stem cell collection appeared to be the patient age and the duration of lenalidomide therapy.[33,60] The failure rate of mobilization following lenalidomide therapy has varied significantly between the different studies, likely a reflection of the lenalidomide treatment duration, age of the patient population undergoing stem cell collection, mobilization regimens, and collection targets used. However, data so far do not indicate any impact on the quality of stem cells collected, as reflected in the engraftment kinetics as well as success.[12,55,56]

The effect of bortezomib on the ability to collect stem cells has also been examined in the context of phase 2 and 3 trials examining the combinations (Table 1).[17,21,49,61] Although no definite impact of initial therapy on stem cell harvest was demonstrated in the smaller phase 2 studies of bortezomib and dexamethasone,[21] in the IFM 2005/01 trial comparing bortezomib/dexamethasone to VAD there was a trend toward lower CD34 numbers among those receiving bortezomib.[17] In contrast, in the HOVON-65/GMMG-HD4 randomized phase 3 trial comparing bortezomib, adriamycin, dexamethasone (PAD) versus VAD as induction treatment, no impact of the regimen was seen on the ability to collect stem cells.[62] No significant impact of initial therapy has been seen in other trials that have combined the novel agents, bortezomib in combination with either lenalidomide or thalidomide.[51,63] Addition of alkylating agents to the initial therapy, especially in combination, may increase the risk of collection failures, but no comparative data are available.[48,49] In a phase 2 study looking at the combination of lenalidomide with cytoxan and dexamethasone for newly diagnosed myeloma, we observed 8 of 30 failures at mobilization.[48] In contrast, in a phase 2 study of cytoxan, bortezomib, and dexamethasone by Reeder et al, all patients who attempted stem cell collection were able to get enough cells for at least one transplantation.[49]

Although there has been a wide spectrum of reported data on the initial therapy with a novel agent and the ability to collect stem cells, some common themes have emerged. In the 2 larger experiences published to date of lenalidomide therapy prior to harvest, the number of cycles of therapy appears to be important.[33,60] Although none of the patients with fewer than 6 cycles of lenalidomide failed to collect stem cells in the Mayo Clinic series, more than 3 cycles of lenalidomide were associated with a higher risk in the M. D. Anderson series. However the smaller studies have not demonstrated such a relationship, and in the absence of detailed data from the larger prospective studies, it would be reasonable to assume that longer duration of therapy will increase the risk of failure. Another common finding has been the age of the patients, with more than one study demonstrating increased likelihood of failure in the older patients.[33,60] In these 2 studies, no relationship was noted between the time off lenalidomide prior to

stem cell harvest. Another important finding across the studies has been the low incidence of collection failure among patients mobilized with chemotherapy, typically cyclophosphamide, and G-CSF.[58,59] Among 28 treatment-naive patients treated with the combination of clarithromycin, lenalidomide, and dexamethasone (BiRD) reported by Mark et al, sufficient stem cells for 2 autologous stem cell transplantations were collected from all patients mobilized with CTX plus G-CSF, versus 33% mobilized with G-CSF alone, demonstrating that this approach can potentially overcome the impairment in stem cell mobilization associated with lenalidomide.[58] For patients failing initial attempts at stem cell mobilization with G-CSF alone, chemotherapy + G-CSF approach appears to have a reasonable efficacy. Five of 7 patients failing G-CSF alone were successfully mobilized with CTX + G-CSF in one study[57] and 18 of 21 patients were remobilized successfully with a chemotherapy + G-CSF approach in another study.[60] Mazumder et al also reported 3 patients who failed to collect successfully despite undergoing mobilization with the CXCR4 inhibitor plerixafor, but were subsequently collected using a combination of cyclophosphamide and G-CSF.[55]

Potential mechanisms of the impact of lenalidomide treatment on stem cell collection

The exact mechanism why lenalidomide inhibits stem cell mobilization is not clear. Koh et al investigated the effects of lenalidomide, pomalidomide (CC4047) (IMiDs), and thalidomide on CD34$^+$ hematopoietic progenitors. They showed in human colony formation assays and long-term culture-initiating cell tests that IMiDs and thalidomide are not toxic to hematopoietic stem cells and do not inhibit self-renewal capacity of stem cells.[64] This makes it less likely that a direct toxic effect of lenalidomide on hematopoietic progenitors explains the limitation in stem cell collection. The group further showed that IMiDs promote myelopoiesis with a concomitant maturation stop of neutrophil granulocytes by down-regulation of critical transcription factors such as PU.1. This leads to an accumulation of immature granulocytes within the bone marrow compartment and neutropenia in the peripheral blood.[65] Interestingly, the group also observed that the G-CSF secretion is highly up-regulated in cultures of hematopoietic progenitors treated with IMiDs (day 3 of treatment: control 140 pg/mL, lenalidomide 800 pg/mL, CC4047 1500 pg/mL)[64] (S.L., written communication, September 2008). The biologic reason for the strong up-regulation of G-CSF is unknown. It is likely that self-regulatory mechanisms up-regulate G-CSF to overcome the maturation stop of granulocytes. Higher levels of G-CSF might lead to a tachyphylactic response, resulting in resistance to G-CSF mobilization. These findings are also supported by our observation that all other "non–G-CSF–based" mobilization approaches such as CTX and AMD3100 are successful in mobilizing a sufficient CD34$^+$ cell number.

Suggested approach to stem cell collection in patients undergoing initial therapy with novel agents

In June 2008, a panel of experts was convened by the International Myeloma Foundation to address issues regarding stem cell collection for autologous transplantation in patients receiving therapy

with lenalidomide. The following statements reflect the considerations of the panel and the consensus recommendations formulated by the panel. The recommendations take into account the existing data suggesting compromised collection with the newer agents in some of the patients as well as the data, although limited, examining alternate approaches to stem cell mobilization. These recommendations will be revised when additional data become available, enabling us to make more specific recommendations.

First attempt: Given the potential for the novel agents to impact the ability of the stem cell collection, we recommend early stem cell mobilization when SCT is being contemplated immediately or later in the course of disease. Such an approach, after 3 to 4 cycles of initial therapy, is quite feasible given the rapid response seen with the new combinations. However, there exists considerable confusion at this point in terms of the mechanisms mediating the decreased collection as well as the best approaches to prevent this problem, and every effort should be made to enroll these patients in clinical trials evaluating these questions.

Among patients undergoing initial therapy with thalidomide or bortezomib in combination with dexamethasone or among those treated with lenalidomide and dexamethasone who have received fewer than 4 cycles of therapy and are younger than 65 years, G-CSF alone is considered adequate for the initial attempt at mobilizing stem cells, although many centers will continue to use cyclophosphamide and G-CSF as their standard protocol. Among those who have received more than 4 cycles of lenalidomide therapy, one should consider the initial use of cyclophosphamide and G-CSF for mobilization. This suggestion is based on the findings of increased failure risk in this population as well as the reduced risk of failure associated with the use of cyclophosphamide and G-CSF. Although the use of cyclophosphamide in all patients is likely to decrease the risk of failure at first attempt, the recommendation to use G-CSF alone in the former group is driven by the low risk of failure in that group, the increased risks and delay associated with use of cyclophosphamide, and finally the ability to successfully collect with cyclophosphamide and G-CSF in the few patients who fail the initial attempt with G-CSF alone. In patients older than 65 years old, we recommend consideration of reduced-dose cyclophosphamide with G-CSF or G-CSF alone with addition of AMD-3100 before the second leukapheresis if the first leukapheresis results in less than 2 million $CD34^+$ cells/kg. In patients receiving other myelosuppressive drugs in combination with lenalidomide, cyclophosphamide and G-CSF should be considered for the initial attempt as the rate of failure increases in these situations. There are no data supporting additional time off therapy prior to mobilization enhancing the likelihood of a successful mobilization. We do not recommend a minimum period that patients have to be off lenalidomide prior to starting G-CSF for mobilization.

Failed stem cell collection

Among patients receiving initial therapy with lenalidomide-containing regimens failing to collect with G-CSF alone, there are 3 options for the subsequent attempt. The majority of the patients can be collected with cyclophosphamide priming and G-CSF. These patients will be candidates for use of AMD3100, which in combination with G-CSF has been very successful in mobilizing stem cells. Another approach includes the use of a combination of G-CSF and granulocyte-macrophage colony-stimulating factor (10 µg/kg per day subcutaneously for 2 days, followed by G-CSF 16 µg/kg per day subcutaneously until stem cell collection is complete).

Upfront use of plerixafor (AMD3100) in lenalidomide-treated patients

The panel discussed the question of routine use of plerixafor for mobilization in this patient group. It was felt that at this time, without a detailed cost benefit analysis, such a recommendation cannot be made and additional clinical trials specifically addressing its use in these patients will allow us to answer this question. Prospective trials should be conducted to study the use of plerixafor in patients failing to reach certain thresholds for peripheral blood CD34 counts.

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