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Peripheral Blood Progenitor Cells Mobilization in Patients with Multiple Myeloma

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Abstract

Autologous stem cell transplantation (ASCT) is considered the standard therapy for younger patients with newly diagnosed symptomatic multiple myeloma (MM). The introduction into clinical practice of novel agents (i.e.: proteasome inhibitors and immunomodulatory derivatives [IMiDs]) has significantly contributed to major advances in MM therapy and prognosis. These novel agents are incorporated into induction regimens to enhance the depth of response before ASCT and further improve post-ASCT outcomes. Collection of adequate hematopoietic stem cells (HSCs) is necessary for successful autologous transplantation. The mobilizing regimen usually consists of cyclophosphamide or disease-specific agents, in combination with a hematopoietic cytokine, usually G-CSF, which mobilizes HPSCs into the bloodstream, in particular when administered after myelosuppressive chemotherapy. In some patients, the number of mobilized CD34+ cells is not sufficient to perform successful stem cell transplantation due to bone marrow damage by neoplastic proliferation and/or chemoradiotherapy. To improve the collection of CD34+ cells, the mobilization procedure can be repeated or an alternative chemotherapy regimen can be chosen. Recently, the new drug plerixafor (Mozobil®) has been introduced to increase the number of circulating CD34+ cells. Its use increases the level of functional HPCs in the peripheral blood, with long-term resettlement

Keywords: Stem cell transplantation; Chemotherapy; Granulocyte-colony stimulating factor; Multiple myeloma; Stem cell mobilization

Introduction

High-dose chemotherapy, supported by autologous hematopoietic stem cell transplantation (ASCT), is an effective treatment strategy for a variety of hematologic malignancies [1-4]. The collection of adequate numbers of HSCs is a prerequisite for proceeding to autologous transplantation; however, approximately 5% to 40% of patients do not meet the minimum threshold of 2×106 CD34+ cells/kg that is associated with timely engraftment [5-9].

The goal of CD34+ cell mobilization is to collect enough cells to achieve a rapid and sustained hematopoietic recovery after high-dose therapy, since delayed hematopoietic recovery correlates with increased toxicity and transplant-related mortality. It has been demonstrated that high CD34+ cell doses (>3/5×10^6/kg) are associated with faster hematological recovery and lower incidence of infectious and bleeding complications [10]. Doses <2×10^6/kg are associated with slower recovery and worse outcomes. CD34+ cell doses over 15×10^6/kg after high-dose melphalan administration can eliminate severe thrombocytopenia. The International Myeloma Working Group (IMWG) has suggested a minimum target of 4×10^6 and, if feasible, an average of 8–10×10^6/kg that should be collected, allowing most myeloma patients to undergo two autografts during the course of their disease, also considering that in some patients, the first ASCT can be unsuccessful [11].

A variety of mobilization strategies are currently used, including growth factors alone or in combination with chemotherapy and, more recently, the partial CXC chemokine receptor-4 (CXCR-4) agonist, plerixafor. Of the available growth factors, the most commonly used is the recombinant granulocyte-colony stimulating factor (G-CSF) analog, filgrastim [12]. Other growth factors include pegfilgrastim, a polyethylene glycol conjugate of G-CSF; lenograstim, glycosylated recombinant G-CSF; molgramostim, recombinant granulocyte macrophage colony-stimulating factor; sargramostim, glycosylated granulocyte macrophage colony-stimulating factor; and ancestim, recombinant human stem cell factor. Lenograstim is widely used for HSC mobilization in Europe; sargramostim, molgramostim, and ancestim are rarely used for mobilization today.

A combination of chemotherapy along with growth factor is a commonly used strategy for mobilization. Chemotherapy is added to improve CD34+ cell yield [13,14], for in vivo purging of mobilized tumor cells to reduce tumor burden (although there are limited supportive data), and to show chemosensitivity before transplantation. However, approximately 30% of patients undergoing a mobilization strategy that includes chemotherapy will develop neutropenic fever [15], and many of those will require hospitalization. The most commonly used chemotherapy regimens include cyclophosphamide at a variety of doses, particularly in patients with multiple myeloma (MM) [16,17]. Mobilization regimens for patients with lymphoma are varied and include ifosphamide, carboplatin, and etoposide, dexamethasone, doxorubicin, cytarabine, and cisplatin (DHAP), etoposide, methyl prednisolone, cytarabine, and cisplatin and others [18,19].

In some patients, the number of mobilized CD34+ cells is not sufficient to perform successful stem cell transplantation due to bone marrow damage by neoplastic proliferation and/or chemoradiotherapy. To improve the collection of CD34+ cells, the mobilization procedure can be repeated or an alternative chemotherapy regimen can be chosen. Recently, in patients with non-Hodgkin lymphoma (NHL) or multiple myeloma (MM) with a poor yield of CD34+ cells, the new drug plerixafor (Mozobil®) can be administered before apheresis to increase

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the number of circulating CD34+ cells. Plerixafor is a derivative of bicyclam, reversible and selective antagonist of the CXCR4 chemokine receptor that acts by blocking the binding between this receptor expressed on hematopoietic stem cells and its ligand, namely the stromal cell-derived factor-1α (SDF-1α), also called CXCL12, expressed on stromal cells. Its use increases the level of functional HPCs in the peripheral blood, with long-term resettlement [20-24].

Therapeutic Strategies in MM Untreated Younger Patients

Induction therapy followed by ASCT has been regarded as standard therapy for younger patients with good health condition [25]. Patients who are considered potential candidates for ASCT receive 2-4 cycles of a non-melphalan-containing regimen and then proceed to stem cell harvest [26]. Subsequently many patients undergo ASCT. However, depending on the response to initial therapy and the patient's choice, initial therapy can be resumed after stem cell harvest, delaying ASCT until first relapse. The role of early versus delayed ASCT is an argument of debate [27]. In the novel agent era, the issue of early versus late ASCT needs to be reevaluated in the context of large randomized clinical trials [28].

On the contrary, the second ASCT in patients who do not achieve almost a Very Good Partial Response (VGPR) after the first transplant seems to be the best option [29].

The introduction of novel agents into the induction regimens significantly improves the outcome of patients with newly diagnosed MM [30], probably because of increased rates of immunophenotypic and/or molecular remissions compared with that reported in the recent past.

The role of Bortezomib, the first proteasome inhibitor used in clinical practice in MM, alone and in combination with dexamethasone (VD), was initially explored in patients who were either eligible or ineligible for ASCT [31]. VD shows superior response rates when compared with vincristine/doxorubicin/prednisone (VAD) with a VGPR rate of 38% vs. 15% after induction therapy in young patients. The higher VGPR rate was confirmed after transplantation (54% vs. 37%), with a PFS improvement (36 vs. 30 months) [32], but the improvement of OS has not been revealed. Sensory neuropathy is the most frequent bortezomib-related toxicity [33]. Studies that compared the 3 drug combination bortezomib/thalidomide/dexamethasone (VTD) with thalidomide/dexamethasone (TD) or VD [34,35] have shown the ability of VTD plus double ASCT followed by bortezomib-based consolidation to overcome the poor prognostic effects of t(4;14) translocation [35]. After three cycles of induction therapy, VTD was superior to TD with respect to all categories of response, including CR, CR-nCR (31% vs. 11%), and at least VGPR (62% vs. 28%).

Beyond the best response rates in terms of PFS, it was demonstrated that the use of VTD is particularly useful in patients with acute renal failure as it acts quickly without dose reduction [35]. The addition of thalidomide, lenalidomide, or cyclophosphamide to bortezomib and dexamethasone has been associated with high response rates and longer progression-free survival (PFS). The three drug-combination bortezomib/cyclophosphamide/dexamethasone (CyBorD or VCD) and the four-drug combination bortezomib/cyclophosphamide/lenalidomide/dexamethasone (VCRD) [36] have been studied in the randomized phase 2 trial EVOLUTION [37] in newly diagnosed myeloma patients. VCD was well tolerated with similar activity compared with the combination bortezomib/lenalidomide/dexamethasone (VRD), a combination which produces remarkably high overall and complete response rates [38]. The CR was achieved in 22% and 47% of patients treated with two different schedules of VCD versus 24% of patients treated with VRD. Although highly active, CR rates with VCRD were similar compared with either VCD or VRD. In newly diagnosed MM, TD produces response rates of 65%-75% [39]. Two randomized trials found TD to be superior to dexamethasone alone [40]. In the transplant setting, there are some trials which aim to clarify the role of lenalidomide as induction therapy [41]. Although its use during induction determines good response rates, it seems to impact on the mobilization of stem cells [42-44].

Allogeneic transplantation (allo-SCT) is an alternative therapy that may improve survival for very high risk and selected patients. The role of allo-SCT remains controversial due to the Treatment-Related Mortality (TRM) (10–20%) and Graft-Versus-Host Disease (GvHD) rates. Young patients with High-Risk disease, ISS II and III associated with del 1p/1q gain, t(4;14), del(17p) or t(14;16), in whom projected 4-year PFS and OS do not exceed 11% and 33%, respectively may potentially benefit from allo-SCT. Clinical trials with long-term follow up are important to prove that allo-SCT should not be abandoned in MM [45].

Mobilization Strategies

Growth factors alone

Since only one trial [46] has been conducted in patients with MM, there are much data available on the mobilization with G-CSF alone on patients with lymphomas and solid tumors. The first randomized study Spitzer et al. [47] compared either G-CSF 10 microg/kg/day alone, or G-CSF at the same dose with GM-CSF 5 microg/kg/day in fifty patients with lymphoid or selected solid tumor malignancies. The bone marrow buffy coat and PBSC product mononuclear cell count ($\times 10^8$/kg) and CD34+ cell count ($\times 10^6$/kg) collected by each method of stem cell mobilization was not significantly different indicating that there is no clinical benefit with PBSC products mobilized with the combination of G-CSF and GM-CSF vs. G-CSF alone.

Filgrastim has been compared to molgramostim in non-Hodgkins lymphoma and Hodgkin's disease patients both at a dose of 250 mcg/m^2/day [48]. Sixty-two patients receiving PBSC or BMSC were enrolled in this study. Results indicated that G-CSF and GM-CSF are both effective in priming autologous PBSC or BMSC for collection.

In a randomized study Ataergin et al. [49] compared filgrastim 10 mcg/kg/day to a 25% reduced dose of lenograstim (7.5 mcg/kg/day) in 40 consecutive patients with hematologic malignancies and solid tumors. Successful mobilization with the first apheresis was achieved in 50% patients in the filgrastim group versus 46% patients in the lenograstim group. No significant difference was seen in the median number of CD34+cells mobilized, as well as the median number of apheresis, median volume of apheresis, percentage of CD34+ cells, and CD34+ cell number. Leukocyte and platelet engraftments, the number of days requiring G-CSF and parenteral antibiotics, the number of transfusions were similar in both groups in the post-transplant period. Authors concluded that filgrastim 10 mcg/kg/day and lenograstim 7.5 mcg/kg/day resulted in successful mobilization of CD341 cells in patients undergoing ASCT. In particular, priming with lenograstim at 25% lower dose does not negatively affect the number of CD34 stem cells harvested, or engraftment results and may achieve an economic benefit in regard to G-CSF requirement or number of vials needed for a successful mobilization and ASCT.

One study investigated the addition of stem cell factor (ancestim

20 mcg/kg/day) to filgrastim in 102 patients diagnosed with heavily pretreated lymphoma patients [50]. Authors concluded that based on the increased proportion of patients reaching target yields of PBPC and reduction in the number of leukaphereses required, stem cell factor plus filgrastim can be considered an important mobilization option for heavily pretreated lymphoma patients receiving ablative therapy with PBPC support.

Of the studies that used a non-chemotherapy mobilization strategy, significant improvement in CD34+ cell yield was achieved with plerixafor in combination with G-CSF in patients with MM (11.0 vs. 6.2×106/kg; P<.001) [46] or NHL (5.69 vs. 1.98×106/kg; P<.01) [51].

Growth factors in combination with chemotherapy

The efficacy of the addition of cyclophosphamide to G-CSF in the mobilization procedures have been extensively demonstrated in hematologic diseases and solid tumors [19,52-60]. Of these studies some resulted in a statistically significant improvement in CD34+ cell yield [52,57,58]. In the study by Facon et al. [57], the addition of ancestim resulted in a median CD34+ cell yield of 12.4×10^6/kg compared with 8.2×10^6/kg for cyclophosphamide plus filgrastim without ancestim (P=.007). In the Martinez et al. [58] study, the addition of growth factor (molgramostim) to cyclophosphamide resulted in a significant improvement in median CD34+ cell yield (1.4 vs. 0.5×10^6/kg; P=.0165). Narayanasami et al. [52] reported CD34+ cell yield was improved with cyclophosphamide combined with filgrastim over filgrastim alone (7.2 vs. 2.5×10^6/kg; P=.004).

Moreover, various studies compared combination of non–cyclophosphamide-based chemotherapy plus one or more growth factors [61-70]. In the category of non–cyclophosphamide-based chemotherapy with growth factor, 2 studies found significantly improved CD34+ cell yield with their interventions. In the Copelan et al. [67] study including exclusively patients with NHL, rituximab improved the yield (9.9 vs. 5.6×10^6/kg; P=.021). Doubling the dose of filgrastim improved the CD34+ cell yield in the Demirer et al. [62] study in a heterogeneous group of patients (8.2 vs. 4.7×10^6/kg; P<.0001).

Various studies have been conducted in order to identify the ideal partner for chemotherapy in the mobilization procedures. Kopf B et al have shown that a lower dose of glycosylated G-CSF is as effective as the standard dose of non-glycosylated G-CSF for PBPC mobilization in patients undergoing ASCT [65].

A randomized trial conducted by the Italian group has shown a lower incidence of febrile episodes during the period of neutropenia in MM patients receiving lenograstim versus those administered filgrastim after high-dose cyclophosphamide for stem cell mobilization [71]. Patients treated with cyclophosphamide were randomly assigned to receive filgrastim or lenograstim. The lenograstim group presented not just a significantly higher absolute CD34+ cell number compared with the filgrastim group but also a less number of days (8 days against 9 of the arm B) needed to reach the target threshold of CD34+ cells, while no differences were detected in terms of collection efficacy.

Our group has investigated the role of G-CSF glycosylation [72] that modifies the chemical and biological properties of G-CSF [73]. Our results show that cyclophosphamide in association with lenograstim results in more adequate mobilization, and the HSC collection target is reached more quickly and requires fewer leukaphereses in patients with MM, NHL or HL that are typical candidates for ASCT and for combined mobilization with chemotherapy and G-CSF. The higher efficacy of glycosylated Hu G-CSF was not influenced by the disease nor by dose of cyclophosphamide administered, bone marrow involvement at diagnosis, and radiotherapy.

Although pegfilgrastim is licensed for the prophylaxis of febrile neutropenia after cytotoxic chemotherapy, it is also an effective mobilizer of CD34+ cells. In fact, pegfilgrastim compared favorably with the other G-CSFs after mobilizing chemotherapy for autologous HSC collection. The administration of pegfilgrastim following high-dose therapy and ASCT shortened the time to myeloid recovery when compared with conventional G-CSF. Plasma G-CSF levels were about 1 log higher with pegfilgrastim, but in the setting of autologous ASCT, this did not result into a faster hematopoietic recovery. Only few data are available on the biological effects of pegfilgrastim, which suggest that pegfilgrastim stimulation results in different functional properties of hematopoietic stem and progenitor cells compared with conventional G-CSF [74,75].

Bassi et al. [76] compared the use of this type of growth factor with standard G-CSF in 64 patients with NHL using high-dose chemotherapy. At mobilization chemotherapy, the first 26 patients used unconjugated G-CSF, while the remaining 38 patients received pegfilgrastim. At the time of harvest, 25 patients collected stem cells after the use of G-CSF and 36 in the peg group. No statistically significant differences were observed in median peripheral CD34+ cells mobilized (77 vs. 71 μL) and in collected CD34+ cells (12.3×10^6/kg vs. 9.4×10^6/kg; p=0.76). In the peg group, all patients collected the target CD34+ cells with a single apheresis with a greater proportion of "optimal" mobilizers (83 vs. 64%; p=0.05) showing that a single dose of pegfilgrastim could be a valid alternative to unconjugated G-CSF to mobilize CD34+ cells in lymphoma patients.

Differences in HPSCs mobilization in response to pegfilgrastim compared to lenograstim and filgrastim in patients with MM and lymphomas have been recently evaluated [77]. The results shows that the glycosylated form of G-CSF provides the best results in the mobilization compared to pegylated form and to non-glycosylated form in terms of collection of target HPSCs and the number of leukaphereses required to achieve it. No significant differences among the different diseases in terms of minimum number of CD34+ cells collected and the number of apheresis necessary to achieve the target, ($4–6\times10^6$ CD34+/Kg b.w.) and even among patients treated with 3, 4 or 7 g/m^2 of cyclophosphamide have been shown. An average of two aphereses was sufficient both in patients with and without bone marrow involvement.

All these findings indicate that, despite all the G-CSF are safe in the mobilization procedure, lenograstim may represent the ideal partner of cyclophosphamide for mobilization of PBSCs in patients with MM candidate to autologous transplantation.

CXC chemokine receptor-4 (CXCR-4) agonist, plerixafor

Data from several clinical trials have demonstrated the superiority of new agents either in combination or not with conventional chemotherapy as up-front therapy for newly diagnosed MM young patients [29,32,35,38,42,78-82].

Lenalidomide is a more active analogue of thalidomide. This provides the basis for its role in newly diagnosed MM patients [42,83]. On the other hand, myelosuppression induced by lenalidomide represents the dose-limiting toxicity and requires monitoring during therapy [84].

Prolonged lenalidomide induction therapy has been reported to affect stem cell mobilization. Patients undergoing peripheral blood stem cell mobilization with G-CSF following lenalidomide

induction had significant decrease in total CD34(+) cells collected, average daily collection, and increased number of aphereses [85]. The exact mechanisms by which lenalidomide interferes with stem cell mobilization are not clear. However, it seems that there are no harmful effects on the quality of PBSC collected as denoted by similar engraftment rate across all treatment groups. Sekeres et al. [84] estimated that more than half of patients treated with lenalidomide-based protocols developed grades 3 and 4 cytopenia, mostly neutropenia and thrombocytopenia. Interestingly, it has been shown that patients who develop severe hematologic toxicity are more likely to better mobilize after cyclophosphamide therapy, but mechanisms beyond this clinical evidence remain still obscure. Based on these reports, no more than six months of Lenalidomide including regimen prior to Cyclophosphamide mobilization should be recommended to avoid poor PBSC collection [86].

The recent introduction of plerixafor which increases the number of mobilized circulating hematopoietic stem and progenitor cells when administered with G-CSF may improve PBSC collection and change this scenario.

In December 2008, the FDA approved the use of plerixafor, in combination with G-CSF, to mobilize HSCs from peripheral blood of patients with NHL and MM, who will subsequently undergo an autologous stem cell transplant. This decision was based on evidence from phase I, II and III clinical trials. Clinical data suggest that plerixafor has similar activity in Hodgkin's lymphoma and solid tumors.

Two phase III, multicenter, randomized, double-blind, placebo-controlled studies were performed to compare the safety and efficacy of plerixafor and G-CSF with placebo and G-CSF in the mobilization of CD34+ cells [46,51]. The studies were very similar in design and the results shown that the proportion of patients receiving plerixafor + G-CSF achieving collection target was higher than those receiving placebo + G-CSF. Moreover, the median number of cells mobilized and the increase in collection on days 4 and 5 (pre and post intervention) were significantly higher in the plerixafor arm compared to the placebo arm.

In current clinical practice, the use of plerixafor is limited to difficult to mobilize patients. Data on the success of mobilization in these patient groups can be obtained from the compassionate use program (CUP) trials. In a paper by Duarte et al. [87], 56 patients from Spain and the UK, who were previous mobilization failures i.e. who mobilized less than 2×10^6 CD34+ cells/kg, were enrolled in a CUP. 75% of previous failures were successfully rescued using G-CSF plus plerixafor, and ultimately 35 patients (63%) underwent transplant with an average of $3.1\pm1.2(1.9\text{-}7.7)\times10^6$ CD34+ cells/kg. Remarkably, 71% of patients met the secondary end point of collecting $\geq10\times10^6$ CD34+ cells/kg.

In Germany, Hübel et al. [88] reported on 60 patients (a mix of previously failed mobilizations and predicted poor mobilizers) from 23 centers. In patients receiving 4 days of G-CSF prior to initiating plerixafor, NHL patients mobilized a median of 2.79×10^6 CD34+ cells/kg, MM patients a median of 4.47×10^6 CD34+ cells/kg, and Hodgkin's disease patients a median of 2.41×10^6 CD34+ cells/kg. All patients, irrespective of the underlying disease, needed a median of two apheresis treatments. Other compassionate reports have been similar: Calandra et al. [89] for example, reported that 66% of patients with NHL, MM, and Hodgkin's disease, who had previously failed to mobilize sufficient numbers of CD34+ cells with chemotherapy or cytokine therapy for transplant, could be successfully remobilized with plerixafor and G-CSF.

Additional to failed mobilizers and predicted poor mobilizers, the pre-emptive use of plerixafor may include slow mobilizers of difficult to mobilize patient groups such as myeloma patients pretreated the lenalidomide [90]. Current developments include intravenous mobilization with plerixafor combined with G-CSF in lymphoma patients [91] or combination of plerixafor, G-CSF, and rituximab for B-cell-reductive, chemotherapy-free mobilization in lymphoma [92].

Even though the majority of the clinical trials of plerixafor mobilization focused on patients receiving G-CSF alone, it is clinically well recognized that the administration of chemotherapy, most often high-dose cyclophosphamide with or without other agents prior to growth factor, enhances CD34+ mobilization. The particular type of regimen used varies according to the primary diagnosis, but this strategy has often been utilized for patients who have already failed mobilization with G-CSF alone or who, due to a large tumor burden, may benefit from additional cytoreduction before transplant. The drawbacks of chemotherapy utilization are mainly related to the toxicities and complications derived from the use of chemotherapy itself as well as the increase in the duration and cost of the mobilization regimen. However, chemotherapy-based mobilization is widely used and for some transplant programs represents the standard of care. An important question is whether the addition of plerixafor to a chemotherapy +G-CSF regimen will further improve efficacy.

One feasibility study combining plerixafor and chemomobilization has been published [93]. In this study, 26 MM patients and 14 NHL patients received plerixafor, which resulted in an about 2-fold increase in collection yield after plerixafor injection when compared to the collection on the previous day. However, based on blood CD34+ counts and yields, most of the patients in that trial were standard mobilizers or even good mobilizers. Recently, a small series of patients who mobilized poorly with chemomobilization and received plerixafor [94] suggested efficacy of this strategy. Also, a study including chemomobilized patients receiving plerixafor and with a previous mobilization failure [88] suggest that this combination is effective. An increasing number of studies are evaluating plerixafor administration in conjunction with chemomobilization, showing the acceptance of this approach [95,96].

Due to lower numbers of CD34+ cells mobilized by plerixafor alone than G-CSF alone, the use of plerixafor alone for mobilization would appear limited to patients who are intolerant of G-CSF [97]. Moreover, *up-front* use of plerixafor is currently recommended in only in adult patients with dialysis-dependent renal failure [98].

Finally, the effect of plerixafor plus G-CSF on tumor cell contamination has been investigated in NHL [46,51] and MM patients [99]. Although the total number of patients examined overall was limited, there did not appear to be an increase in tumor cells in the apheresis product following plerixafor above that observed or expected with G-CSF. Thus, contamination of an apheresis product would be expected to be similar to that obtained by standard G-CSF mobilization.

Conclusion

Initial therapy for MM depends on the eligibility for ASCT. Patients who are considered potential candidates for ASCT receive 2-4 cycles of a non-melphalan-containing regimen and then proceed to stem cell harvest. Several factors may influence mobilization outcome, including age, stage disease, prior chemotherapy (e.g., fludarabine or melphalan), irradiation or a higher number of prior treatment lines. In MM G-CSF cytokines alone (filgrastim, lenograstim) or in combination with chemotherapy (cyclophosphamide or etoposide) are indicated for PBSC mobilization. The use of new drugs for the

induction therapy leads good response rates, although affecting the mobilization of stem cells. PBSC mobilization can be optimized with an appropriate individualized strategy. Eg, in patients older than 65 years and those who have previously received more than 4 cycles of lenalidomide-containing regimens, stem cells must be mobilized with either cyclophosphamide + G-CSF or with plerixafor. The choice of the appropriate mobilization regimen, based on disease stage, and the apheresis protocol optimization can improve the mobilization outcome.

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