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Effects of bone marrow or mesenchymal stem cell transplantation on oral mucositis (mouse) induced by fractionated irradiation

The early radiation response of oral mucosa is a frequent and severe adverse effect of radio(chemo)therapy for advanced head-and-neck tumors [8, 19, 20, 47]. Oral mucositis significantly affects the patients' quality of life [20, 31]. Oral discomfort and swallowing difficulties can lead to dehydration and weight loss. An increased risk of local and systemic infections is the consequence of the breakdown of the mucosal barrier. Mucositis-related unplanned treatment interruptions can result in decreased local tumor control [3, 4, 18, 28, 38, 40]. The early mucosal reaction also increases the risk for late effects in the oral cavity [14]. Moreover, the oral radiation response has a significant socio-economic impact [19, 33]. Despite the high relevance of this early adverse effect, prophylaxis and management currently only focus on improving oral hygiene and standard supportive care [27, 31, 39, 44].

A beneficial effect of circulating, non-embryonic bone marrow derived or mesenchymal stem cells with regard to regeneration after injury was shown for various organs [2, 30, 34, 37, 43, 48]. In mouse tongue mucosa, in contrast, no effect of bone marrow transplantation in combination with single dose irradiation was observed, while stem cell mobilization with G-CSF significantly reduced ulcerative oral mucositis (Schmidt et al., submitted).

The present study was initiated to define the potential of adult stem cell transplantation to ameliorate radiation-induced oral mucositis during fractionated irradiation. Whole bone marrow (BM) or isolated mesenchymal stem cells (MSC) were administered.

All experiments were performed in mouse tongue mucosa. As a clinically relevant endpoint, mucosal ulceration, corresponding to confluent mucositis in patients, was analyzed. Daily fractionated irradiation (5×3 Gy/week) was administered over 1 or 3 weeks. All protocols were concluded by test irradiation with graded doses to generate complete dose–effect curves, as an indicator of the residual tissue tolerance. Stem cell therapy was applied at various time points from before the onset of irradiation (day –1) until week 3 (day +15).

Materials and methods

All experiments were performed according to the current animal welfare legislation with permission of the respective governmental authorities (Regierungspräsidium Dresden/Landesdirektion Sachsen).

Animals and housing

For all experiments, female mice of the inbred C3H/Neu strain, provided by the breeding facility of the Medical Faculty Carl Gustav Carus, Technical University of Dresden, were used. The animals were housed under specified pathogen-free conditions with controlled conditions of temperature (21–24°C) and humidity (50–60%). An automated light program regulated a 12/12-h light/dark rhythm, with lights on from 06:30 to 18:30 h Central European Time. The mice were kept in size 3 Makrolon® cages, maximum ten per cage, on sawdust bedding. Standard mouse diet and filtered city tab water were provided ad libitum.

Irradiation technique

The techniques for the mucosal irradiation have been described in detail elsewhere [1, 16, 17, 23, 25]. In brief, irradiation of the mucosa was performed by a combination of two techniques: percutaneous fractionated treatment of the entire snout and local irradiation of a 3×3 mm^2 test area at the lower tongue surface. The latter was used for single dose and test irradiation.

For *snout irradiation* an "Isovolt 320/13" X-ray device (Seifert Röntgenwer-

Tab. 1 Effect of bone marrow (BM) transplantation on mouse tongue reactions in combination with fractionated irradiation over 1 or 3 weeks

Number of fractions	Day of BM transplantation	Number of transplanted cells	$ED_{50} \pm \sigma$ (Gy)	p_{dose}	$p_{vs.\ control}$	Latent time ± SD (days)	Ulcer duration ± SD (days)
5×3 Gy/1 week							
5	–	–	7.1±1.2	0.0003	–	6.7±0.5	2.9±0.7
5	–1	3×10^6	8.9±1.8	0.0006	0.0559	7.9±0.6	2.5±0.5
5	–1	6×10^6	9.8±0.8	0.0011	0.0011	6.3±0.7	3.2±0.7
5	+2	3×10^6	7.9±1.6	0.0003	0.3361	7.0±0.5	3.1±0.7
5	+2	6×10^6	7.5±0.6	0.0024	0.4010	6.2±0.5	3.2±0.7
5	+4	3×10^6	8.7±1.6	0.0002	0.0646	6.4±0.7	3.1±0.8
5	+4	6×10^6	10.0±0.8	0.0006	0.0007	6.3±0.6	3.3±0.6
15×3 Gy/3 weeks							
15	–	–	7.9±2.7	0.0027	–	5.0±0.6	3.0±0.5
15	–1	6×10^6	9.3±1.1	0.0007	0.0576	7.1±0.6	2.3±0.5
15	+2	6×10^6	9.1±1.1	0.0007	0.1044	7.1±0.5	2.3±0.5
15	+4	6×10^6	11.1±2.0	0.0018	0.0059	8.8±0.9	2.5±0.5
15	+8	6×10^6	10.8±0.9	0.0012	0.0044	6.4±0.5	2.2±0.4
15	+11	6×10^6	11.0±1.0	0.0009	0.0029	6.5±0.5	2.3±0.4
15	+15	6×10^6	12.4±0.9	0.0017	0.0001	7.2±0.7	2.1±0.3

Tab. 2 Effect of mesenchymal stem cell (*MSC*) transplantation on mouse tongue reactions in combination with 1 or 3 weeks of fractionated irradiation

Number of fractions	Day of MSC transplantation	$ED_{50} \pm \sigma$ (Gy)	p_{dose}	$p_{vs.\ control}$	Latent time ± SD (days)	Ulcer duration ± SD (days)
5×3 Gy/1 week						
5	–	7.5±2.2	0.0012	–	10.2±1.0	3.6±1.6
5	–1	9.9±0.7	0.0033	0.0109	7.8±0.7	2.8±0.6
5	+2	11.6±0.9	0.0018	0.0002	7.9±0.8	2.8±0.6
5	+4	9.3±1.7	0.0004	0.0804	9.1±0.7	2.7±0.6
15×3 Gy/3 week						
15	–	9.5±1.8	0.0011	–	9.4±0.6	2.6±0.5
15	+8	10.9±1.3	0.0021	0.1806	8.7±0.7	3.5±1.5

ke, Ahrensburg, Germany) was operated at 200 kV with a tube current of 20 mA; a beam filter of 0.6 mm Cu and 1 mm Al was used. For immobilization, the non-anesthetized animals were immobilized in plastic tubes. The bodies of the mice were shielded with 1.5 cm lead equivalent. The treatment field encompassed the snouts including the entire tongue.

Local irradiation (test irradiation) was given to a treatment field at the central lower tongue using a DARPAC 150-MC X-ray device (Forward Raytech Ltd, Swindon, UK), operated at 25 kV with a tube current of 20 mA. Immobilization of the animals for test irradiation was achieved by intraperitoneal administration of pentobarbitone sodium at a dose of 60 mg/kg. The mice were placed in a supine position in the central bore of an aluminum block. The tongue was guided through a hole (3 mm diameter) in the roof of the block, and the upper tongue surface fixed to the outer surface of the block. A 3×3 mm^2 window in a 1 mm thick aluminum plate, placed centrally over the tongue, defined the treatment field.

Whole bone marrow (BM) was obtained from 8–12 week old male mice of the Dresden C3H/Neu colony. After cervical dislocation, their femura were removed, both ends of the femoral shaft were clipped and the bone marrow was flushed with 0.5 ml PBS containing 1% FCS. Cell numbers were determined using a Neubauer counting chamber. For transplantation 3×10^6 or 6×10^6 cells in a volume of 0.2 or 0.4 ml were injected into the tail vein of female recipient mice.

Mesenchymal stem cells (MSC) were isolated at the Laboratoire d'Hématopoïése of the University Francois–Rabelais, Tours, France, from freshly prepared bone marrow from male mice of the Dresden C3H/Neu colony. After isolation of CD45-negative cells, the three-lineages (adipocyte, osteocyte, chondrocyte) differentiation potential of these cells was controlled. The cells were subsequently returned to Dresden and subcultured. For transplantation 3×10^6 cells were injected into the tail vein of female recipient mice.

Experimental design

Fractionated irradiation and test irradiation

Daily fractionated irradiation (3 Gy/day) was given over 1 (days 0–4) or 3 weeks (days 0–4, 7–11, 14–18). The residual mucosal radiation tolerance was defined by graded local test doses (5 dose groups with 10 animals each) on days 7 or 21, respectively. These test doses were grouped around the expected ED_{50} value in steps of ±2 and ±5 Gy.

Stem cell transplantation

In combination with fractionated irradiation over 1 week, the number of transplanted BM cells was 3×10^6 or 6×10^6, respectively. BM was administered on day –1, +2 or +4. With daily fractionated irradiation over 3 weeks 6×10^6 cells were injected on day –1, +2, +4, +8, +11 or +15. MSC transplantation (6×10^6 cells) was performed on day –1, +2 or +4 during one, or on day +8 during 3 weeks of fractionation. The reduced schedule was based on the low availability of MSC.

The 1-week and 3-week fractionation experiments with transplantation of bone marrow (BMT) and the mesenchymal stem cells transplantation experiments (MSCT), including all control experiments, were performed independently by different investigators (J.H., A.S., R.N.). All control experiments were hence carried out in duplicate.

Follow-up, endpoint, and statistical analysis

Radiation-induced changes of the oral mucosa were scored daily from the onset of first symptoms until complete re-epithelialization, during immobilization by pentobarbitone sodium (~45 mg/kg intraperitoneally). Mucosal ulceration was analyzed as the clinically relevant endpoint, as defined by the unequivocal clinical appearance of the mucosa (glossy pseudomembrane). Time course parameters were latent time (local irradiation to first ulcer diagnosis) and ulcer duration (first diagnosis until re-epithelialization). Un-blinded scoring was done by J.H. (MSCT), A.S. (BMT, 1-week studies) and R.N. (BMT, 3-week studies).

For all statistical procedures, the Statistical Analysis System, SAS, version 9.2 was used [41]. Dose-effect relationships were established by standard logit analyses (SAS PROC PROBIT, logit function) [24, 41], revealing ED_{50} values (doses, at which an ulcer is expected in 50% of the animals) and their standard deviation σ, and p values for the effect of dose on ulcer induction. For the comparison of dose–effect relationships, a likelihood ratio test based on the logit model was used [41, 42].

Results

Control experiments

In **Tab. 1** the results for the test irradiation after 1 (5×3 Gy) or 3 weeks (15×3 Gy) of fractionation are summarized.

Effect of bone marrow transplantation

The results of bone marrow transplantation (BMT) are summarized in **Tab. 1**; the ED_{50} values are illustrated in **Fig. 1 and Fig. 2**. Transplantation of 3×10^6 BM cells during 1 week of fractionation resulted in a slight decrease of the incidence of mucosal ulceration, with a statistical trend for days −1 and +4 only. Transplantation of 6×10^6 BM cells on day +2 did not significantly alter the ulcer incidence. In contrast, administration of the increased cell number on days −1 and +4 significantly reduced the sensitivity to test irradiation.

Abstract · Zusammenfassung

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Effects of bone marrow or mesenchymal stem cell transplantation on oral mucositis (mouse) induced by fractionated irradiation

Abstract

Background and purpose. Oral mucositis is a severe and dose limiting early side effect of radiotherapy for head-and-neck tumors. This study was initiated to determine the effect of bone marrow- and mesenchymal stem cell transplantation on oral mucositis (mouse tongue model) induced by fractionated irradiation.

Material and methods. Daily fractionated irradiation (5×3 Gy/week) was given over 1 (days 0–4) or 3 weeks (days 0–4, 7–11, 14–18). Each protocol was terminated (day 7 or 21) by graded test doses (5 dose groups, 10 animals each) in order to generate complete dose–effect curves. The incidence of mucosal ulceration, corresponding to confluent mucositis grade 3 (RTOG/EORTC), was analyzed as the primary, clinically relevant endpoint. Bone marrow or mesenchymal stem cells were transplanted intravenously at various time points within these fractionation protocols.

Results. Transplantation of 6×10^6, but not of 3×10^6 bone marrow stem cells on day −1, +4, +8, +11 or +15 significantly increased the ED_{50} values (dose, at which an ulcer is expected in 50% of the mice); transplantation on day +2, in contrast, was ineffective. Mesenchymal stem cell transplantation on day −1, 2 or +8 significantly, and on day +4 marginally increased the ED_{50} values.

Conclusion. Transplantation of bone marrow or mesenchymal stem cells has the potential to modulate radiation-induced oral mucositis during fractionated radiotherapy. The effect is dependent on the timing of the transplantation. The mechanisms require further investigation.

Keywords

Oral mucositis · Fractionated radiotherapy · Bone marrow transplantation · Mesenchymal stem cells · Mouse tongue model

Einfluss von Knochenmarks- oder mesenchymaler Stammzelltransplantation auf die orale Mukositis (Maus) bei fraktionierter Bestrahlung

Zusammenfassung

Hintergrund und Ziel. Die orale Mukositis ist eine schwere und dosislimitierende frühe Nebenwirkung der Strahlentherapie von Kopf-Hals-Tumoren. Ziel der vorliegenden Arbeit war die Untersuchung des Effekts der Transplantation von Knochenmarks- oder mesenchymalen Stammzellen auf die durch fraktionierte Bestrahlung induzierte orale Mukositis im Modell der Mäusezunge.

Material und Methoden. Die tägliche fraktionierte Bestrahlung (5-mal 3 Gy/Woche) wurde über eine (Tage 0–4) oder über 3 Wochen (Tage 0–4, 7–11, 14–18) appliziert. Abschließend erfolgte die lokale Bestrahlung (Tag 7 oder 21) in gestaffelten Testdosen (5 Dosisgruppen mit je 10 Tieren) zur Generierung kompletter Dosis-Effekt-Kurven. Die Inzidenz von Schleimhautulzera, entsprechend einer konfluenten Grad-3-Mukositis (RTOG/EORTC), wurde als primärer, klinisch relevanter Endpunkt analysiert. Knochenmark oder mesenchymale Stammzellen wurden zu verschiedenen Zeitpunkten während dieser Fraktionierungsprotokolle intravenös transplantiert.

Ergebnisse. Die Transplantation von 6×10^6, nicht jedoch von 3×10^6 Knochenmarkszellen, an den Tagen −1, +4, +8, +11 oder +15 der fraktionierten Bestrahlung erhöhte die ED_{50}-Werte (Dosis, bei der bei 50% der Tiere ein Schleimhautulkus zu erwarten ist) signifikant; im Gegensatz dazu war die Transplantation an Tag +2 wirkungslos. Die mesenchymale Stammzelltransplantation führte an den Tagen −1, +4 oder +8 zu einer signifikanten und an Tag +4 zu einer marginalen Erhöhung der ED_{50}-Werte.

Schlussfolgerung. Die Transplantation von Knochenmark bzw. mesenchymalen Stammzellen hat das Potential, die durch Strahlentherapie induzierte orale Mukositis zu beeinflussen. Dieser Effekt ist abhängig vom Zeitpunkt der Transplantation. Die Mechanismen bedürfen einer weiteren Abklärung.

Schlüsselwörter

Orale Mukositis · Fraktionierte Strahlentherapie · Knochenmarkstransplantation · Mesenchymale Stammzellen · Mäuse Zungenmodell

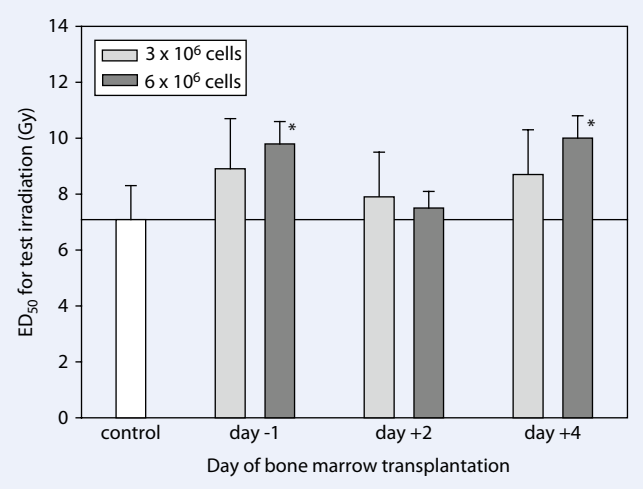

Fig. 1 ▲ ED_{50} values for test irradiation after 1 week of fractionated irradiation in combination with bone marrow transplantation. ED_{50} values, i.e., doses at which ulcers are expected in 50% of the mice, and their standard deviation σ (error bars) were computed by logit analysis; they were based on complete dose–effect curves with five dose groups, ten animals each. Comparison of the dose–effect curves was performed by a likelihood ratio test on the basis of the logit model (*p<0.05). The day of bone marrow transplantation is indicated on the abscissa

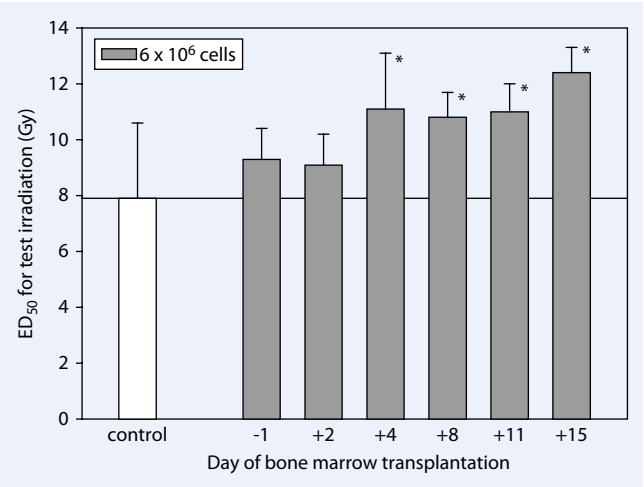

Fig. 2 ▲ ED_{50} values for test irradiation after 3 weeks of fractionated irradiation in combination with bone marrow transplantation. Bone marrow transplantation was carried out on days indicated at the abscissa. Error bars represent the standard deviation σ of the ED_{50} values, as computed by probit analysis (*p<0.05)

With fractionated irradiation over 3 weeks, administration of 6×10^6 BM cells on day +2 did not significantly increase residual radiation tolerance; a trend was observed for day –1. However, transplantation at any later time points during fractionated irradiation resulted in significantly decrease in ulcer incidences, with a systematic indication of a more pronounced effect at the latest time points. No systematically or clinically relevant changes were observed in the time course parameters of the response (**Tab. 1**).

Transplantation of mesenchymal stem cells

The results of mesenchymal stem cell transplantation (MSCT) are summarized in **Tab. 2**; the ED_{50} values are illustrated in **Fig. 3**. MSCT with 1 week of fractionated irradiation on day –1 and +2 increased the residual tolerance of the oral mucosa significantly, while only a trend was found for day +4. In combination with 3 weeks of fractionation MSC transplantation on day +8 yielded a significant effect. No systematically or clinically relevant changes were observed in the time course parameters of the response (**Tab. 2**).

Discussion

Oral mucositis is the most important and dose-limiting early side effect of radiotherapy of advanced head and neck tumors [8, 47]. The ulcerative response of the oral epithelium is considered to be the result of the sterilization of tissue stem cells with the ability to completely restore the mucosa after irradiation [10, 11, 15]. Bone marrow is an important source of (easily accessible) stem cells, which have a significant potential to form a variety of tissue-specific cells. Bone marrow stem cells are capable of replenishing all blood cell lineages [7, 46]. However, their immunomodulatory properties may potentially also promote regeneration of other tissues [6, 26]. Mesenchymal stem cells have been identified in the BM as multipotent progenitor cells with a potential to differentiate into various cell types [9, 22, 29, 36]. They are essentially involved in wound healing [32].

This paper for the first time reports results of preclinical experiments on the effect of stem cell transplantation on the oral mucosal response to fractionated irradiation. All experiments have been performed in mouse tongue mucosa as a well-established animal model. The results of all control experiments were in excellent accordance with those of previous studies. The clinical identification of mucosal ulceration is unequivocal, as illustrated by the excellent agreement of the independent control experiments. The experiments were performed like others before in an unblinded design, which, however, did not impact on the results, as none of the investigators had any interest in a particular outcome.

In the control experiments, the isoeffective doses for test irradiation after 1 and 3 weeks of fractionation were virtually similar—despite additional 10×5 Gy in

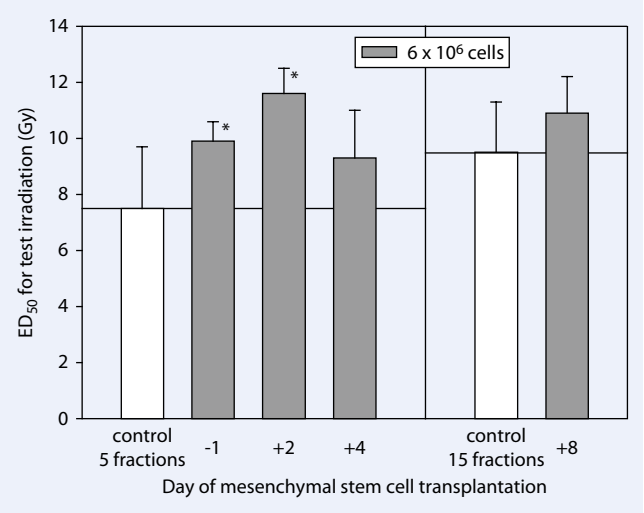

Fig. 3 ▲ ED_{50} values for test irradiation after fractionated irradiation over 1 or 3 weeks combined with mesenchymal stem cell transplantation. The bars represent the ED_{50} values for the test irradiation; error bars their standard deviation σ as calculated by logit analyses (*p<0.05). The "control" bars illustrate the ED_{50} for test irradiation after fractionated treatment without transplantation of mesenchymal stem cells

the latter protocol. This demonstrates, in excellent accordance with previous studies [1, 13, 23, 35], that the entire fractionated dose in weeks two and three was completely compensated by radiation-induced repopulation [10, 11].

BMT increased the mucosal radiation tolerance only if the number of transplanted cells was high. BMT with $6{\times}10^6$ cells highly significantly increased isoeffective doses, except for day +2. MSCT yielded similar results for day –1 and day 8, but only a marginally significant effect for day +4. A clear difference between the two cell types was observed for transplantation on day +2. In complete contrast to the present experiments, BMT in combination with single dose irradiation did not have any effect (Schmidt et al., submitted).

Significant differences in the effect of stem cell therapy have been observed between the various irradiation protocols, particularly single dose vs. fractionated exposure. Moreover, these differences were dependent on the time points of stem cell administration during daily fractionation. This clearly demonstrates the complexity, with dose- and time-dependent factors, of the (still hypothetical) mechanisms through which the stem cells may act. Moreover, the differences between the two transplantation strategies, i.e., BMT vs. MSCT, particularly on day +2 of fractionated irradiation, indicate cell type specificity of the protective mechanisms.

At present, insights into these underlying biological mechanisms of the protective effect of adult stem cells are lacking. The assumption that stem cells in a novel (damaged) microenvironment would transdifferentiate and produce tissue-specific cells is discussed controversially [5, 45]. In the mouse tongue model, when male stem cells were administered to female animals, no clonal representation of the transplanted cells was found by in situ hybridization of the Y chromosome (Schmidt, unpublished). Moreover, overall cell numbers in oral mucosa were identical in the stem cell transplanted and the only irradiated mice (data not shown). Hence, clonal expansion of homed cells is an unlikely mechanism.

Two alternative mechanisms of action may be considered: (1) homing of individual circulating stem cells into the damaged tissue and mediation—without clonal proliferation—of tissue regeneration through paracrine factors, or (2) release of regeneration-promoting factors by circulating stem cells [12]. The former mechanism may be based on a low number of homed cells. After single dose irradiation of skin, transplanted MSC only constituted 0.25% of the cells [21]. However, it needs to be emphasized that the discussion of potential mechanisms of stem cell effects are purely speculative.

Conclusion

This is the first investigation in which stem cell transplantation for amelioration of normal tissue effects of radiotherapy, here oral mucositis, was carried out in combination with fractionated irradiation. The beneficial effect is dependent on the number of stem cells, the timing of administration, and the stem cell type administered. Further mechanistic studies are required to optimize stem cell based strategies for amelioration of normal tissue effects in fractionated radiotherapy.

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Compliance with ethical guidelines

Conflict of interest. M. Schmidt, J. Haagen, R. Noack, A. Siegemund, P. Gabriel, and W. Dörr state that there are no conflicts of interest.

All national guidelines on the care and use of laboratory animals have been followed and the necessary approval was obtained from the relevant authorities.

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