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The Role of Platelet-Rich Plasma in the Prevention of Chemotherapy-Induced Alopecia

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Alopecia is a distressing side effect of chemotherapy. Patients who experience hair loss due to their chemotherapy treatment have been shown to have decreased social functioning, impaired body image, and be at an increased risk of developing depression [1]. No effective prevention for this significant side effect has been established, with the result that some patients either refuse a treatment or choose one that is less efficacious [2]. Chemotherapy-induced alopecia (CIA) occurs with various chemotherapeutic agents, but most prominent are alkylating agents (cyclophosphamide), antitumor antibiotics, antimicrotubule agents, and topoisomerase inhibitors (etoposide).

The mechanisms by which chemotherapy induces alopecia have been studied extensively but are not completely understood. It has been found that the normal hair follicle cycle is disrupted, leading to a process known as effluvium [3]. Anagen is the first stage of hair growth during which the highly vascularized hair bulb, which contains the mitotically active dermal papilla and hair matrix, gives rise to new hair. When the chemotherapeutic agent reaches the hair follicle through the surrounding blood vessels, the hair matrix cells undergo apoptosis, causing the hair to separate at the bulb and be shed. This shedding can occur during the anagen phase or the telogen phase [3]. The primary mechanism of hair loss, however, is anagen effluvium which occurs because, at any time, 80–90% of all hair is in the anagen phase and hair in this phase is more susceptible to the effect of chemotherapeutic agents due to the actively dividing cells. Furthermore, CIA can be either temporary or permanent, depending on the level of damage to the stem cells located in the bulb. These stem cells give rise to new hair, so if the damage is extensive hair regrowth is unlikely.

Studies have shown a significant improvement in androgenic alopecia with the use of blood products such as platelet-rich plas-

Table 1. Protection from chemotherapy-induced alopecia by platelet-rich plasma or mononuclear cells

Chemotherapy	Test group	Rats, <i>n</i>	Protection at the site of s.c. injection			
			0	1+	2+	3+
Ara-C	control	6	0	0	0	6
	PRP	6	0	0	0	6
	MC	6	6	0	0	0
VP-16	control	6	0	0	0	6
	PRP	6	0	0	0	6
	MC	6	0	0	0	6
CTX	control	6	0	0	0	6
	PRP	6	0	0	0	6
	MC	6	0	0	0	6

Group 1 received Ara-C, 25 mg/kg/day i.p. for 7 days. Group 2 received VP-16, 1.5 mg/kg i.p. on days 11–13. Group 3 received Cytosin (CTX), 37.5 mg/kg i.p. on day 11. In addition, each subgroup received treatments of control PBS 0.1 mL, platelet-rich plasma (PRP) 2×10^5 platelets in 0.1 mL, or mononuclear cells (MC) 1×10^5 cell in 0.1 mL. All injections were given s.c. on the top of the head. The groups receiving Ara-C received the treatments for 7 consecutive days (days 7–13), those receiving VP-16 were treated for 5 consecutive days (days 9–13), and those receiving CTX were treated for 3 consecutive days (days 9–11). Results were recorded 10 days after the last day of chemotherapy. 0 = no alopecia, 1+ = 25–50% alopecia, 2+ = 50–75% alopecia, 3+ = 75–100% alopecia at s.c. site of testing.

ma (PRP) [4]. The mechanism of follicular stimulation of PRP is unknown, but it is hypothesized that it is linked to growth factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) [4]. Another blood component of interest for follicular protection is the mononuclear cells (MC). MC produce large amounts of IL-1, which has been shown to have protective effects against CIA [5]. Despite these previous findings, no studies have been conducted on the effect of PRP and MC on CIA. Due to this absence of studies, the effect of PRP and MC for protection from CIA was studied in a well-developed young rat model [5] (i.e., the inbred Fisher rat, Envigo Labs). This model has been previously used to identify potential protective agents in rats that translate to human clinical trials [6].

The chemotherapeutic agents investigated were cytosine arabinoside (Ara-C), etoposide (VP-16), and Cytosin (cyclophosphamide). Ara-C was used due to its progressive alopecic effect when

Fig. 1. Representative photograph and histology from Ara-C and VP-16 treated groups (1 rat from each treatment group). **A–C** All rats received Ara-C i.p. for 7 days. **D–F** Rats received VP-16 i.p. for 3 days. **A, D** Rats also received treatments of control PBS 0.1 mL, platelet-rich plasma (PRP) 2×10^5 platelets in 0.1 mL, or mononuclear cells (MC) 1×10^5 cells in 0.1 mL. All these injections were given s.c. on the top of the head. The groups receiving Ara-C received the treatments for 7 consecutive days (days 7–13) and those receiving VP-16 were treated for 5 consecutive days (days 9–13).

Pictures and biopsies were taken 10 days after the last day of chemotherapy. MC only protected against Ara-C-induced alopecia (**C, c'**). However, PRP offered no protection from any of the chemotherapies used. **a', b', d'–f'** Formalin-fixed, paraffin-embedded sections of skin (from the area indicated by the arrow) demonstrate chemotherapy-induced hair follicle damage 10 days later. $\times 100$. **c'** In contrast, the histopathology demonstrates healthy hair follicles in anagen. $\times 40$. Scale bar, 100 μm .

used in low concentrations over the course of 7 days. Although Ara-C is not used alone in the clinical setting of cancer treatment, it is a useful tool for identifying potential agents with protective effects against CIA [5]. Two experimental groups and 1 control group were studied for each of the chemotherapies listed above.

For each chemotherapeutic agent, 18 rats were split into 3 groups of 6 rats each. All of the treatments were given as 0.1-mL intraperitoneal (i.p.) injections. Three groups received VP-16, 1.5 mg/kg i.p. for 3 consecutive days (days 11–13), another 3 groups received Cytosar, 37.5 mg/kg i.p. on day 11, and the final 3 groups

received Ara-C, 25 mg/kg for 7 consecutive days (days 7–13). The treatment groups were given either PRP or MC in 0.1-mL subcutaneous (s.c.) injections at the top of the head and the control groups were given 0.1 mL of PBS s.c. at the same location. The groups receiving VP-16 received the treatments for 5 consecutive days (days 9–13), those receiving Cytosan were treated for 3 consecutive days (days 9–11), and those receiving Ara-C were treated for 7 consecutive days (days 7–13).

The blood components were harvested from inbred Fisher rats (retired breeders) and were prepared fresh for every treatment. For PRP preparation, blood was collected by cardiac puncture post-mortem in sodium citrate solution to prevent coagulation, and then centrifuged at 800 rpm for 10 min. A platelet count was performed, showing $>2 \times 10^6$ platelets/mL, 0.1 mL of which was then injected. The MC were harvested from the peritoneum and injected at a concentration of 1×10^5 cells/injection, comprising 80% monocytes, 15% lymphocytes, 4% neutrophils and 1% basophils.

To analyze the results, pictures and samples for histopathology were taken 10 days after the last injections (Fig. 1). Additionally, samples of PRP and MC were analyzed using a mouse IL-1 β ELISA immunoassay (Sigma-Aldrich). This assay measures the expression of IL-1 in the samples compared to a standard preparation. The results indicated a 5.5-fold increased expression of IL-1 from the samples of MC compared to PRP.

Although PRP has been hailed as a promising agent for hair regrowth [7], it did not offer any protection from CIA. Importantly, there was no protection observed in the groups receiving Ara-C only, a mild chemotherapeutic agent for which protection is more readily achieved. The study only demonstrated protection from CIA in the group of rats given Ara-C treated with MC (Table 1; Fig. 1). This effect is mediated by IL-1 and has been previously demonstrated [8], therefore serving as a positive control.

Additionally, no enhanced regrowth was seen in the groups treated with PRP. One could argue that manipulation of the PRP preparation, concentration, and timing may alter its effectiveness, but the concentration and preparation used were what are currently being used in clinical practice. Furthermore, there was no indication of any protective effect by PRP, upon physical observation or by pathological analysis in any of the 6 animals per group. In this model, triplicates are sufficient to determine if there is a signal of effect.

In conclusion, protection was only seen in the Ara-C group treated with MC. This protective effect, likely mediated by IL-1, has been previously demonstrated and thus served as a good control for cellular therapy in this study. There have been no previous experiments involving PRP and its protective potential against CIA, so these results are the first to demonstrate PRP's lack of protective ability against CIA.

Statement of Ethics

All animal experiments conducted in this original study were approved by the University of Miami Institutional Animal Care and Use Committee.

Disclosure Statement

The authors declare no conflicts of interest.

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