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Effect of Radiotherapy on HB Level and Nutritional Status of Tumor Patients and Its Relationship with Hepcidin and EPO

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Abstract: We studied the expression features of Hepcidin (HEP), Erythropoietin (EPO), Albumin (ALB) and Prealbumin (PA), and the pathogenesis of anemia in tumor patients caused by radiotherapy. We tested the hemoglobin (HB) concentration in 446 cancer patients who received radiotherapy, and measured the serum HEP, EPO, ALB and PA n 92 cases to explore the pathogenesis of anemia caused by radiotherapy. The results were: (1) The HB level before and after radiotherapy in 446 patients were 119.85±19.87g/L and 116.32±24.25g/L (t=2.5211, P<0.05). The cases of anemia before and after radiotherapy were 146 cases and 175 cases (χ^2=4.09, P<0.05). (2) The HB level before and after radiotherapy in 92 patients and in 20 cases of control group were respectively 127.33±17.12, 119.41±17.05 and 132.80±11.80g/L, the difference was statistically significant (F=11.70, P<0.01). The anemia cases were 14 and 27, respectively, which were also statistically significant (χ^2=8.68, P<0.01). (3) The HEP level before and after radiotherapy in 92 patients and in 20 cases of control group were 3.38±2.48, 2.37±1.37 and 3.22±1.10mg/mL respectively, the difference was statistically significant (F=3.88, P<0.05). (4) EPO level before and after radiotherapy in 92 patients and in 20 controls were 5.05±3.50, 5.75±1.99 and 3.81±1.15mg/mL respectively, the difference was statistically significant (F=9.18, P<0.01). (5) The levels of ALB and PA before radiotherapy in 92 patients were higher than those after radiotherapy. (6) HEP was negatively correlated with HB before radiotherapy (r=-0.2938, t=2.9089, P<0.01), but HEP was not correlated with HB after radiotherapy (r=- 0.0111, P>0.05). (7) There were positive correlation between ALB and HB before and after radiotherapy (all P<0.01). (8) There were positive correlation between PA and HB before and after radiotherapy (all P<0.01). Therefore, Radiotherapy could cause anemia and deteriorate nutritional status in cancer patients. Anemia negatively feedback inhibited the expression of HEP, while EPO was highly compensatory.

Keywords: Radiotherapy, Anemia, Hepcidin, Erythropoietin (EPO), Tumor, Albumin, Prealbumin

1. Introduction

Anemia is easily caused by undergoing surgery, radiotherapy or chemotherapy in tumor patients, and can also be caused by factors of the tumor itself, the incidence rate of anemia therefore is getting higher and higher [1]. Studies have shown that the abnormal high expression of serum Hepcidin (HEP) caused by the inflammatory response in tumor patients is the main cause of cancer-related anemia [2, 3]. However, there were few studies on the expression of HEP in radiation-related anemia in radiotherapy patients, and its significance remained unclear. In addition, nutritional status is also related to anemia, however there were few relevant studies. Therefore, in this study, 446 cases patients with tumor who recently received radiotherapy in our hospital were prospectively studied. The levels of serum HEP and Erythropoietin (EPO), and Albumin (ALB), Prealbumin (PA) before and after radiotherapy in 92 cases with cancer were determined by double antibody sandwich avidinbiotincomplex-enzyme linked immunosorbent assay (ABC-ELISA) method. The expression characteristics and its significance in the occurrence and development of

radiation-related anemia were analyzed.

2. Materials and Methods

2.1. Subjects

A total of 446 tumor patients with relatively complete data received radiotherapy in our hospital from January to December 2015. There were 298 males and 148 females, ranging from 23 to 80 years old, with an average age of 57.1 years old. Types of diseases include: colorectal cancer 97 cases, bone cancer and metastatic carcinoma 59 cases, breast cancer 59 cases, brain metastasis cancer 40 cases, gynecology cancer 41 cases, lung cancer 36 cases, gastric cancer 27 cases, nasopharyngeal carcinoma 29 cases, esophageal cancer18 cases, cervical metastatic cancer 16 cases, skin cancer 15 cases, lymphoma 13 cases, malignant gliomas 12 cases, prostate gland carcinoma 7 cases, pancreatic cancer 4 cases, testis tumor 3 cases and thymoma 2 cases. A total of 20 healthy subjects were selected as the control group, including 10 males and 10 females, aged from 26 to 46 years old, with an average age of 36.8 years old. The diagnostic criteria for anemia formulated by Hematology Society of Chinese Medical Association were used as the inclusion criteria for this study, that is, hemoglobin (HB) value<120.0g/L for males and<110.0g/L for females. Patients with chronic liver, kidney and other complications significantly affecting iron metabolism were removed.

This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics committee of Taicang Hospital of Soochow University. Written informed consent were obtained from all participants.

2.2. Regents

All testing reagents were purchased from Shanghai Tianyu Technology Co. Ltd., Beckman-Coulter blood cell five classification count detector was used for blood cell detection, and EPO and HEP ELISA device provided by Shanghai Precision Instrument Company was used for blood cell detection.

2.3. Research Methods

Blood samples were collected twice before and after radiotherapy (30-45 days after radiotherapy), divided into three tubes. One tube was immediately tested for blood cells, and the other two tubes were stored in a refrigerator at -80°C after specimen collection, and then collected together for the detection of HEP and EPO by ABC-ELISA. ALB and PA were tested by Siemens automatic biochemical analyzer.

2.4. Statistical Analysis

SPSS19.0 software package was used for statistical analysis. One-way ANOVA F test, pair-wise Q test, chi-square test, t-test and Pearson correlation analysis were adopted according to the nature of the data.

3. Results

3.1. Serum Levels of HB Before And After Radiotherapy in 446 Patients with Cancer

Serum levels of HB before and after radiotherapy in 446 patients with cancer were shown in Table 1. The relationship among anemia and the radiotherapy location and measurement were shown in Table 2.

Table 1. *Serum levels of Hb before and after radiotherapy in 446 patients with cancer.*

	HB (g/L)	Anemia cases (n)	Degree of anemia			
			I	II	III	IV
Pre- radiotherapy	119.85±19.87	146	75	55	12	4
Post- radiotherapy	116.32±24.25	175	90	65	14	6
Statistical analysis	t=2.5211*	χ^2=4.09*	χ^2=0.05			

Note: *P<0.05, others all were P>0.05.

Table 2. *The relationship among anemia and the radiotherapy location and measurement in 446 patients with cancer.*

Item		n	Pre- radiotherapy	Post- radiotherapy	χ^2
RT Location	Vertebral body, thoracic and pelvic cavity	255	108	135	5.73*
	Other locations	191	38	40	0.06
RT Measurement	≥45GY	332	112	139	4.67*
	<45GY	114	34	36	0.28
Chemotherapy	Yes	321	126	151	3.97*
	No	125	21	24	0.44
Age	≥60 years	249	87	109	4.07*
	<60 yeas	197	59	66	0.57
Sex	Male	298	62	79	2.68
	Female	148	84	96	2.04

Note: (1)* P<0.05, others all were P>0.05. (2) RT: Radiotherapy.

3.2. Serum Levels of EPO, HEP, ALB, PA and HB Before and After Radiotherapy in 92 Patients with Cancer

Serum levels of EPO, HEP, ALB, PA and HB before and after radiotherapy in 92 patients with cancer were shown in Table 3 and Table 4. There were statistically significant differences between 92 patients before and after radiotherapy and 20 patients in HB, EPO and HEP control groups (F=11.70, P<0.01; F=9.18, P<0.01, F=3.88, P<0.05). The ALB and PA levels of before were higher than those after radiotherapy (all P<0.01). There were 14 cases of anemia before and 27 cases of anemia after radiotherapy in the 92 patients, and the differences between them were statistically significant (χ^2=8.68, P<0.01).

Table 3. *Comparison of serum EPO, HEP, ALB, PA and HB levels pre- and post-radiotherapy in 92 patients (x±s).*

Item	pre-RT	post-RT	control group	F	pre-therapy/CP (q)	post-CP (q)	pre-/post-therapy/(q)
HB (g/L)	127.3±17.12	119.4±17.05	132.8±11.80	11.70 **	3.76 *	4.40 *	6.42 **
EPO (mg/ml)	5.05±3.50	5.75±1.99	3.81±1.15	9.18 **	3.97 *	3.68 *	6.03 **
HEP (mg/ml)	3.38±2.48	2.36±1.37	3.22±1.10	3.88 *	0.47	2.43	4.81*
ALB (g/L)	40.82±3.93	37.65±5.52	41.15±3.19	5.61**	0.59	5.33**	4.96**
PA (mg/L)	206.23±50.92	157.60±54.89	209.31±45.71	7.91**	1.12	5.36**	5.48**

Note: (1)*P<0.05, **P<0.01, the others were all>0.05. (2) CP: control group. RT: Radiotherapy

Table 4. *The actual serum levels of EPO, HEP and HB in patients with and without anemia before and after radiotherapy.*

Project	Pre-radiotherapy		*t* value	Post-radiotherapy		*t* value
	Anemia (n=14)	Non-anemia (n=78)		Anemia (n=27)	Non-anemia (n=51)	
HB (g/L)	98.57±12.04	132.49±12.04	9.7225**	101.56±1.56	128.86±10.71	10.4198**
EPO (mg/ml)	5.00±1.13	4.40±2.45	0.8960	75.90±2.23	5.66±1.88	0.5040
HEP (mg/ml)	4.73±2.76	3.13±2.37	2.2714*	2.37±1.38	2.38±1.37	0.0305

Note: *P<0.05, **P<0.01, the others were all>0.05.

3.3. The Correlation Analysis Between HB, EPO and HEP Levels

The correlation analysis between HB, EPO and HEP levels before and after radiotherapy was carried out. Results showed that (1) There was a negative correlation between HEP and HB before radiotherapy (r=-0.2938, t=2.9089, P<0.01), and there was no correlation between HEP and EPO or EPO and HB (r=0.1234 and -0.0111, all P>0.05). (2) There was no correlation between HEP and HB, HEP and EPO, or EPO and HB after radiotherapy (r=-0.1289, 0.0355, 0.0546, all P>0.05). The specific results were in Table 5.

Table 5. *The results of correlation analysis.*

Item	Pre- radiotherapy		post- radiotherapy	
	r	t	r	t
HEP/HB	-0.2938	2.9089**	-0.1289	1.2347
EPO/HB	-0.0111	0.1053	0.0546	0.5180
ALB/HB	0.4608	4.9125**	0.5533	6.3018**
PA/HB	0.3901	4.0216**	0.4267	4.4724**

Note: **P<0.01, the others were all>0.05.

4. Discuss

Our study showed that HB level before radiotherapy were significantly lower than that after radiotherapy and were related to the location of radiotherapy, dosage, simultaneous chemotherapy and the age of the patients. This result suggested that radiotherapy did have an effect on the hematopoietic system of tumor patients, consistent with the results reported in the literature [4, 5]. At the same time, the nutritional indicators ALB and PA were both significantly lower after radiotherapy than before, indicating that radiotherapy can also deteriorate the nutritional status of patients. In addition, ALB and PA were both positively correlated with HB, suggesting that the deterioration of nutritional status could cause or aggravate anemia, which was also consistent with literature [6, 7].

Anemia can be caused by tumor patients' own factors such as hemorrhage and malnutrition as well as intervention measures such as surgery, radiotherapy and chemotherapy, so the incidence of anemia is high, even up to 90% [1-3, 8]. In this study, the number of anemia cases after radiotherapy was significantly higher than that before radiotherapy, and the actual HB level after radiotherapy was also significantly lower than that before radiotherapy and the control group, which was consistent with the results of literature both native and foreign [9-11], indicating that radiotherapy does have inhibitory or damage effects on the hematopoietic system.

Existing studies both native and foreign have shown that inflammatory mediators, especially HEP, play an important role in the occurrence and development of tumor-related anemia [12]. In this study, it was found that HEP decreased gradually with the aggravation of anemia (i.e. the decrease of HB level), and the HEP level after radiotherapy was significantly lower than that before radiotherapy and the control group. At the same time, there was a negative correlation between HEP and HB level before radiotherapy, while there was no correlation between HEP and HB level after radiotherapy, suggesting that it was the direct damage and suppression of bone marrow caused by radiotherapy that led to anemia in tumor patients, rather than the systemic inflammatory response caused by radiotherapy. This

was completely different from the mechanism of the high expression of HEP resulting from the systemic inflammatory response caused by surgery, chemotherapy and the tumor itself, which could lead to anemia. Previous studies of iron-deficiency anemia found that the expression of HEP decreased with the decrease of HB level, because anemia can negatively inhibit the expression of HEP [13, 14]. This study showed that the expression characteristics of HEP were consistent in patients with radiation-associated anemia and iron-deficiency anemia.

EPO is a cytokine that can regulate red blood cell production. We found that with the prolonging of radiotherapy, the level of HB decreased continuously (that was, the aggravation of anemia) while the level of EPO increased gradually. EPO levels were consistently higher than those in the normal control group. This result was consistent with the literature [15]. This indicated that this was the compensatory reaction of the body after the occurrence of anemia, which could promote the body to hematopoiesis and enhance the level of HB, so as to correct or improve anemia.

At the same time, this study also found that there was no correlation between HEP and EPO levels, which was consistent with our previous research results [10-12]. This is because HEP is an important factor leading to anemia in tumors or other chronic inflammatory diseases. In other words, HEP is the triggering mechanism of tumor-related anemia, while EPO is the body's compensatory response after anemia occurs in patients. Of course, the exact relationship between HEP and EPO level needs further in-depth and rigorous study.

In conclusion, radiotherapy does damage the hematopoietic function of bone marrow and can cause anemia in patients with radiotherapy. With the decrease of HB level, HEP gradually decreased and lost its original negative correlation with HB level. Therefore, to fully understand the damage of radiotherapy to the body's hematopoietic system and the change characteristics of HEP and EPO expression is of great clinical significance in ensuring the successful completion of radiotherapy, improving the cure rate of tumor and improving the quality of life, which is worthy of further study.

5. Conclusion

Radiotherapy could cause anemia and deteriorate nutritional status in cancer patients. There were positive correlations between HB and ALB and PA before and after radiotherapy, but there was negative correlation between HEP and HB before radiotherapy, and no relationship between HEP and HB after radiotherapy. Anemia negative feedback inhibited the expression of HEP, while EPO was highly compensatory.

Disclosure Statement

No potential conflict of interest was reported by the author (s).

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