An evaluation of combining reinfusing concentrated ascitic fluid and OK-432 therapy in patients with intractable malignant ascites

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key words : ascites, reinfusion treatment of cell-free concentrated autogenous ascites, OK-432

〈Abstract〉

We have performed a total of 356 intravenous reinfusions of ascites in 91 cases of malignant ascites encountered at our hospital. These patients were refractory to treatment with various drugs including diuretics. Ascitic drainage by paracentesis was performed in another 30 cases.

The following findings were obtained : 1. Intravenous reinfusion of ascites was a more useful clinical therapy than drainage of ascites by paracentesis. 2. The therapeutic effect of intravenous reinfusion of ascites tended to be increased when it was combined with biological response modifiers (BRM) such as OK-432. 3. The combined administration of OK-432 with intravenous reinfusion of ascites was not so different between subcutaneous and intraperitoneal routes of administration. 4. The combination of anti-cancer agents with the intravenous reinfusion of ascites failed to improve the therapeutic effect. 5. Fever was the main side effect of this therapy. It was well tolerated with appropriate antipyretics.

Introduction

Ascites which seen in the terminal stage of malignant tumor and painful to the patient is often refractory to various treatments. We have reported on our favorable results of intravenous reinfusion of autologous ascites after filtration and concentration (hereunder referred to as intravenous reinfusion of ascites) in such cases¹⁻⁶⁾.

The present paper reports the effect of combination therapy of intravenous reinfusion of ascites with anti-cancer agents, with importance attached to the clinical usefulness of combination therapy with OK-432, a biological response modifier (hereunder referred to as BRM).

Subjects

We have performed intravenous reinfusion of ascites in 91 cases of ascites due to malignant tumor, who were refractory to treatment with various drugs including diuretics for a total of 356 times at our hospital from March 1984 through December 1988. Their primary diseases included gastric cancer in 33

cases, hepatoma in 24 cases, colon cancer in 9 cases, gall bladder cancer in 8 cases, pancreatic cancer in 5 cases, ovarian cancer in 5 cases, lung cancer in one case, breast cancer in one case, duodenal cancer (papillary region) in one case, malignant lymphoma in one case, omental tumor in one case, gastric cancer and hepatoma in one case, and unknown origin in one case. On the other hand, ascitic drainage by paracentesis was performed in 30 cases consisting of gastric cancer in 15 cases, hepatoma in 7 cases, ovarian cancer in 4 cases, and cancer of the large intestine, the gall bladder, the bile duct, and unknown origin in one case each. There were no differences in age, underlying disease, and the stage of cancer among the groups of patients treated by ascites drainage by paracentesis, single intravenous reinfusion of ascites, and its combination with anti-cancer agents and/or BRM.

Methods

As reported previously¹⁾, the method of intravenous reinfusion of ascites was as follows. Ascites was

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[Received for publication June 20, 1989 and in revised form November 20, 1990]

collected by peritoneal paracentesis from the patients, and it was stored temporarily in a bag for collection. The fluid was filtrated and removed of bacteria as well as cellular components including cancer cells in ascites through PVA filter which was made of polyvinylalcohol with 330 μm in thickness, and had micropores of less than 0.2 μm in diameter. Then it was concentrated with CELA filter which was made of cellulose with 200 μm in internal diameter and 8 μm in thickness. This concentrate was placed in a bag for reinfusion to be given back over 2~4 hours by intravenous infusion. In an attempt to prevent febrile response, intravenous administration of concentrated ascites was carried out with a screen filter (SQ40S) which was made of polyester mesh with 40 μm in diameter³⁾.

On the other hand, ascites drainage by paracentesis was a simple removal by peritoneal paracentesis without reinfusion of ascites.

Anti-cancer agents consisting of mitomycin C, adriamycin, cisplatin, 5-fluorouracil, UFT, cyclophosphamide, cytarabin, peplomycin and etoposide were additionally given in 50 cases of reinfusion group systemically or by the intra-arterial or intraperitoneal route. Such BRM as OK-432, PSK, ubenimex and lentinan were also given in 46 cases of reinfusion group. When OK-432 was used as BRM, it was given subcutaneously (daily-weekly) by gradual increments from 0.2KE up to 5KE, and/or intraperitoneally just after drainage of ascites at a dose of 10KE or 20KE. PSK and ubenimex were given daily per os, and lentinan was given weekly by the intravenous route.

Results

As reported previously¹⁾, efficacy of intravenous reinfusion of ascites and ascites drainage by paracentesis was classified into the following 5 groups depending upon the time interval between one treatment and the next similar treatment.

Group A : Not less than one month

Group B : From two weeks to one month

Group C : From one week to two weeks

Group D : Less than one week

Group E : Undeterminable

Of groups A through D which were determinable, groups A through C were taken as effective and the efficacy rate was obtained by $A+B+C/A+B+C+D$.

1. Comparison of intravenous reinfusion of ascites with ascites drainage by paracentesis (Table 1)

Intravenous reinfusion of ascites was performed in 91 cases with the efficacy classification as follows : 16 cases in Group A, 11 cases in Group B, 19 cases in Group C, 40 cases in Group D, and 5 cases in Group E ; 46 effective doses in total with an efficacy rate of 53.5%. The mean survival time of all 91 cases resulted in 62 ± 102 days ($m \pm SD$).

On the other hand, ascites drainage by paracentesis performed in 30 cases resulted in one case in Group A, zero case in Group B, one case in Group C, 26 cases in Group D, and 2 cases in Group E ; totally, there were 2 effective cases with an efficacy rate of 7.1%. The mean survival time resulted in 20 ± 19 days ($m \pm SD$).

It was found that the former method was clearly more useful than the latter.

2. Comparison of the single intravenous reinfusion of ascites with that with various combination therapies (Table 2)

Out of the 91 cases treated with intravenous reinfusion of ascites, 28 cases received it alone and the other 63 cases received it in combination with anti-cancer agents and/or BRM.

1) Effect of the single intravenous reinfusion of ascites

Efficacy classification for the 28 cases receiving intravenous reinfusion of ascites alone was 4, 2, 7, 14, and 1 case in Groups A, B, C, D, and E, respectively, resulting in 13 effective cases at an efficacy rate of 48.1%.

2) Effect of intravenous reinfusion of ascites in combination with anti-cancer agents

Intravenous reinfusion of ascites was given in combination with anti-cancer agents in 17 cases with the resultant efficacy classification of 3, 3, 1, 8 and 2 cases in Groups A, B, C, D, and E, respectively, or 7 effective cases at an efficacy rate of 46.7%. There was no difference between reinfusion alone and this combination therapy.

3) Effect of intravenous reinfusion of ascites in combination with BRM

Intravenous reinfusion of ascites was given in combination with BRM in 13 cases with the resultant efficacy classification of 4, 2, 3, 3, and 1 case in Groups A, B, C, D, and E, respectively, or 9 effective cases at

Table 1 Comparison of intravenous reinfusion of ascites with ascites drainage by paracentesis. Classification of efficacy and mean survival time after each treatment.

	Reinfusion		Paracentesis	
	No. of cases (%)		No. of cases (%)	
	91		30	
A	16	(17.6)	1	(3.3)
B	11	(12.1)	0	(0)
C	19	(20.9)	1	(3.3)
D	40	(43.9)	26	(86.7)
E	5	(5.5)	2	(6.7)
Effectiveness	46	(53.5)	2	(7.1)
	p < 0.01			
Survival time (m±SD)	62±102 days		20±19 days	
	p < 0.001			

an efficacy rate of 75 %. The results seemed to be superior to those of the above two treatments, but statistical difference was not shown.

4) Effect of intravenous reinfusion of ascites in combination with anti-cancer agents and BRM

Intravenous reinfusion of ascites was given in combination with anti-cancer agents and BRM with the resultant efficacy classification of 5, 4, 8, 15 and 1 in Groups A, B, C, D, and E, respectively, or 17 effective cases at an efficacy rate of 53.1 %. The results were similar to those of reinfusion alone and combination with anti-cancer agents.

3. Effect of intravenous reinfusion of ascites in combination with OK-432 (Table 3)

Of BRM used, OK-432 most often employed was analyzed in regard to its combined effect by the route of administration.

1) Effects of intravenous reinfusion of ascites in combination with OK-432 alone

OK-432 alone was given in combination with intravenous reinfusion of ascites in 11 cases by the intraperitoneal route in 7 cases, subcutaneous route in 3 cases, and intraperitoneal and subcutaneous routes in 1 case.

Efficacy classification for the 8 cases receiving intraperitoneal administration alone and in combination with subcutaneous administration was 3, 2, 1, 2, and 0 cases in Groups A, B, C, D, and E, respectively, or 6 effective cases at an efficacy rate of 75 %.

On the other hand, efficacy classification for the 4

cases receiving subcutaneous administration alone and in combination with intraperitoneal administration was 2, 1, and 1 in Groups A, C, and E, respectively, or effective in all 3 cases where it was possible to judge. The above results indicated that the combination of intravenous reinfusion of ascites with OK-432 gave favorable results without regard to its route of administration.

2) Effect of intravenous reinfusion of ascites in combination with OK-432 and anti-cancer agents

In 30 cases of intravenous reinfusion of ascites, OK-432 and anti-cancer agents were given as a combination therapy. OK-432 was given intraperitoneally in 12 cases, subcutaneously in 13, and intraperitoneally and subcutaneously in 5 of the 30 cases. Efficacy classification for the 17 cases of intraperitoneal administration alone and in combination with subcutaneous administration was 4, 0, 4, 8, and 1 case in Groups A, B, C, D, and E, respectively, or 8 effective cases at an efficacy rate of 50 %.

On the other hand, efficacy classification for the 18 cases of subcutaneous administration alone and in combination with intraperitoneal administration was 1, 4, 4, 9, and 0 cases in Groups A, B, C, D, and E, respectively, or 9 effective cases at an efficacy rate of 50 %. These results were similar to those of intravenous reinfusion of ascites alone and in combination with anti-cancer agents.

4. Side effect of this therapy

Table 2 Comparison of the single intravenous reinfusion of ascites with that with various combination therapies.

	Reinfusion only		Reinfusion + Anti-cancer agents		Reinfusion + BRM		Reinfusion + Anti-cancer agents + BRM	
	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)
	28		17		13		33	
A	4	(14.3)	3	(17.6)	4	(30.8)	5	(15.2)
B	2	(7.1)	3	(17.6)	2	(15.4)	4	(12.1)
C	7	(25.0)	1	(5.9)	3	(23.1)	8	(24.2)
D	14	(50.0)	8	(47.1)	3	(23.1)	15	(45.6)
E	1	(3.6)	2	(11.8)	1	(7.6)	1	(3.0)
Effectiveness	13	(48.1)	7	(46.7)	9	(75.0)	17	(53.1)
NS								
NS								
NS								

Table 3 Effect of intravenous reinfusion of ascites in combination with OK-432

	Reinfusion only		Reinfusion + OK-432 i. p.		Reinfusion + OK-432 s. d.		Reinfusion + Anti-cancer agents		Reinfusion + Anti-cancer agents + OK-432 i. p.		Reinfusion + Anti-cancer agents + OK-432 s. d.	
	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)
	28		8		4		17		17		18	
A	4	(14.3)	3	(37.5)	2	(50.0)	3	(17.6)	4	(23.5)	1	(5.6)
B	2	(7.1)	2	(25.0)	0	(0)	3	(17.6)	0	(0)	4	(22.2)
C	7	(25.0)	1	(12.5)	1	(25.0)	1	(5.9)	4	(23.5)	4	(22.2)
D	14	(50.0)	2	(25.0)	0	(0)	8	(47.1)	8	(47.1)	9	(50.0)
E	1	(3.6)	0	(0)	1	(25.0)	2	(11.8)	1	(5.9)	0	(0)
Effectiveness	13	(48.1)	6	(75.0)	3	(100)	7	(46.7)	8	(50.0)	9	(50.0)
NS												
NS												
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As previously reported³⁾, SQ40S could not completely prevent transient fever (higher than 38°C, within 24hrs just after the reinfusion of ascites) though it could decreased significantly the incidence of febrile reaction. In some cases, we could not determine whether this febrile response was due to the reinfused ascites or the combined agents such as OK-432. But, it was well tolerable with appropriate antipyretics even in such cases.

2 cases suffered from acute renal failure after treated with CDDP and intravenous infusion of ascites. No other side effects such as abdominal pain, hypotension, etc, were found in the present study.

Discussion

Possible mechanisms of ascites encountered in patients with advanced terminal cancer are : 1) obstruction of subserosal lymph channels and venules due to tumor cells^{4,6)}, 2) reduced plasma colloid osmotic pressure resulting from malnutrition⁶⁾, and 3) excess fluid production by serosal tumor. Such ascites is often refractory to drug therapy with diuretics, anti-cancer agents, etc., thereby requiring drainage by peritoneal paracentesis. However, mere ascitic drainage by paracentesis causes the simultaneous loss of protein in ascites, promoting the low protein state, and supplementary administration of the plasma protein preparation in large quantities is mandatory in some

occasions. We have reported¹⁻⁵⁾ on the efficacy and safety of intravenous reinfusion of ascites, we have carried out in such cases of terminal cancerous, refractory ascites. In the 91 cases of the present study receiving intravenous reinfusion of ascites, we were able to confirm the efficacy as described above. Intravenous reinfusion of ascites seems to be effective due to such mechanisms as 1) reduced cancer cells in ascites through filtration⁶⁾ and 2) prevention of loss of protein in ascites by ascitic concentration and intravenous reinfusion. In an attempt to increase its effect, the combined effect with chemotherapy and/or BRM was investigated in this report. The 91 cases of intravenous reinfusion of ascites were classified into 4 groups of 1) the single intravenous reinfusion of ascites and its combination with 2) anti-cancer agents, 3) BRM, and 4) anti-cancer agents and BRM. The highest clinical efficacy was seen in the group 3 among these groups, though statistical difference was not shown. In our study, there was no additional therapeutic effect when anti-cancer agents were combined with intravenous reinfusion of ascites.

Advanced terminal cancer patients are generally suffering from insufficient immunity, which is more marked in patients with refractory ascites and in poor systemic condition⁸⁾. Ordinary systemic chemotherapy or radiotherapy in such a case would be detrimental to cellular protective factors in the host in addition to tumor cells at a time, reducing more immunological competence resulting in lethal outcome⁸⁾. Preparations given in such cases of insufficient immunity in anticipation of activating immunity are biological response modifiers (BRM)⁹⁾. We have tried 4 BRM : OK-432, PSK, ubenimex, and lentinan. Of these, OK-432 was used most frequently and we investigated the effect of intravenous reinfusion of ascites in combination with OK-432.

OK-432 is a preparation from hemolytic streptococcus, a representative BRM developed by Okamoto et al¹⁰⁾. It has been already used in clinical practice and its clinical efficacy is well-known in terms of survival prolongation in cancer patients, etc¹¹⁻¹⁶⁾. Although the mechanism of its anti-cancer effect has not been fully elucidated yet, it is accepted that it is mainly host-mediated and activates various host cells represented by macrophages thereby elevating immunological

competence of cancer bearing patients and exerting anti-cancer activity^{18,19)}. When 41 cases of intravenous reinfusion of ascites in combination with OK-432 investigated in the present study were classified into 2 groups of 1) intravenous reinfusion of ascites in combination with OK-432 and 2) that with OK-432 and anti-cancer agents, a higher efficacy rate was seen for the former group as with the results on BRM in general. OK-432 is administrated intracutaneously, subcutaneously, intravenously, intramuscularly, into tumor or body cavity, orally, etc¹¹⁻¹⁷⁾. In the present study, we gave systemic medication by successive subcutaneous administration of 0, 2~5KE every other day to once a week and topical medication by intraperitoneal administration of 10 or 20KE. Although the small number of cases studied would not allow sufficient evaluation, there seems to be no marked difference in clinical efficacy between the groups given OK-432 subcutaneously and intraperitoneally so far as our present investigation is concerned. However, OK-432 has been reported to be more effective by the intraperitoneal than the systemic route in the treatment of refractory ascites in terminal cancer⁸⁾. This remains to be a point for further study.

Fever, anorexia, nausea, and vomiting are reported side effects of OK-432 given systemically¹²⁾. Abdominal pain is also reported in about 25 % of cases medicated intraperitoneally⁶⁾. Of these, fever is the highest in incidence. As intravenous reinfusion of ascites and OK-432 both often cause fever as a side effect, this combination would require a measure against fever of much more importance. The usefulness of screen filter (SQ40S) has been reported as a measure against fever on intravenous reinfusion of ascites³⁾. On the other hand, according to Uchida et al¹²⁾, a high incidence of fever due to intravenous or intramuscular administration of OK-432 could be reduced to 25 % by its intracutaneous administration. According to Torisu et al., fever was noted in about 90 % of cases given OK-432 intraperitoneally but was controlled by the antipyretic in these cases⁶⁾. We also succeeded in controlling fever seemingly due to OK-432 and / or reinfusion of ascites by appropriate administration of antipyretics. In the present study, 2 cases suffered from acute renal failure after treated

with CDDP and intravenous reinfusion of ascites, but it seemed to be due to the nephrotoxicity of CDDP. There were no other side effects of particular significance such as abdominal pain, hypotension, etc, in the present study.

Conclusion

The following findings were obtained in the treatment of refractory ascites in terminal cancer ;

1. Intravenous reinfusion of ascites was a more useful clinical therapy than ascites drainage by paracentesis.
2. Therapeutic effect of intravenous reinfusion of ascites tended to be increased more when combined with BRM such as OK-432.
3. Combined administration of OK-432 with intravenous reinfusion of ascites was not so different between subcutaneous and intraperitoneal routes of administration.
4. The combination of anti-cancer agents with intravenous reinfusion of ascites failed to improve the therapeutic effect.
5. Fever was the main side effect of this therapy. It was well tolerable with appropriate antipyretics.

Acknowledgment : We wish to thank Dr. Teramae N, Dr. Nakamura S, Dr. Kasai T, Dr. Kojima T, Dr. Katoh T for their assistance with this manuscript.

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難治性癌性腹水に対する自家腹水濾過濃縮再静注法とOK-432 の併用効果の検討

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〈要旨〉

利尿剤等の通常の薬物療法にて対処し得ない難治性癌性腹水患者 91 例に対して、延べ 356 回の自家腹水濾過濃縮再静注法を施行し、その臨床的有用性を腹水穿刺単純排液法と比較検討した結果、前者は後者よりはるかに有用であった。

自家腹水濾過濃縮再静注法の治療効果は、OK-432 等の生物学的反応修飾物質 (BRM) を併用すると、さらに高められるように思われた。しかし、自家腹水濾過濃縮再静注法に抗癌剤を併用しても、その治療的効果は上がらなかった。BRM 併用群のうち、特に OK-432 についてその投与方法別 (皮下注射、腹腔内注入) に併用効果を検討したが、明らかな有意差はなかった。

自家腹水濾過濃縮再静注法と OK-432 の併用における主な副作用は一過性発熱であるが、これは適切な解熱剤を投与することにより対処し得た。